

HANDBOOK FOR PRINCIPLES AND PRACTICE OF GYNECOLOGIC ONCOLOGY

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TO OUR MENTORS, WHO INSPIRE US
TO BE BETTER SCIENTISTS, AND OUR
STUDENTS, WHO INSPIRE US TO BE
BETTER TEACHERS

The role of textbooks in general and handbooks in particular is in transition as a wide array of online and continually updated sources of medical information are available to trainees, who are often more computer savvy than their teachers. However, approaching a totally new area of knowledge remains a daunting task. Commonplace terms are confusing, and the detail necessary for day-to-day clinical judgments obscures the larger picture. This handbook is designed for students, residents, nurses, and those new to gynecologic oncology who need to rapidly acquire basic familiarity with the field and would like all critical information in one place. The chapters have been shortened from the key chapters in the parent textbook, *Principles and Practice of Gynecologic Oncology*, 5th Edition, with an emphasis on introductory and summary information rather than details of clinical trials. We have highlighted key points so that the most important information stands out. Although a few suggested articles for reading are listed in each chapter, references are largely in the parent textbook. When required, trainees can move easily from chapters in this handbook to the comprehensive chapters in the larger textbook for greater detail.

We hope this handbook will serve new practitioners as a convenient introduction to a field that is exciting and changing rapidly—and that they will find it as rewarding as we have.

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CHAPTER 1 ■ PRINCIPLES OF CHEMOTHERAPY IN GYNECOLOGIC CANCER

PHARMACOLOGIC PRINCIPLES OF CHEMOTHERAPY

KEY POINTS

- Oral agents may have variable absorption depending on the patient's intake of food and grapefruit juice.
- Both cisplatin and paclitaxel are used intraperitoneally; cisplatin is well absorbed into the systemic circulation, but paclitaxel is not, necessitating the coadministration of intravenous paclitaxel when paclitaxel is given intraperitoneally.
- Carboplatin, one of the most commonly used chemotherapy agents, is dosed based on renal function; attention must be paid to clinical factors that artificially lower creatinine, such as the acute postoperative state, as this might result in overdosing.
- Cytochrome P450 (CYP)-3A4 inhibitors such as ketoconazole will raise concentrations of agents, such as paclitaxel, that are metabolized by CYP-3A4. CYP-3A4 inducers, for example, glucocorticoids, will decrease concentrations of such agents.

Absorption, Distribution, and Transport

Drugs may be given orally, intravenously, intramuscularly, intra-arterially, or intraperitoneally. The increasing utilization of oral chemotherapy and the development of oral molecular-targeted agents have renewed interest in bioavailability in the setting of meals and other factors that can modulate local intestinal transport. For example, the bioavailability of one tyrosine kinase inhibitor was increased over threefold in the setting of a high-fat meal. Another interesting association concerns grapefruit juice, which can alter absorption through the intestinal mucosa by inhibiting the cytochrome P450 isozyme, cytochrome P450 (CYP)-3A4, and possibly the drug efflux pump, P-glycoprotein. Drugs that are substrates for either of these compounds can be more efficiently absorbed after the ingestion of grapefruit juice due to reduced local metabolism, leading to increased serum levels.

The extent of drug binding to serum proteins may have an impact on tumor drug exposure. Many chemotherapeutic agents are lipophilic and highly protein bound in plasma, particularly to albumin. It is generally the unbound “free” drug that mediates toxicity, and any condition associated

with variability in protein binding can have an impact on cumulative drug exposure. For example, the toxicity of chemotherapy is frequently accentuated in patients with poor nutritional status, which is associated with reduced protein levels.

Intraperitoneal Chemotherapy

Intracavitary chemotherapy has been used for tumors confined to the peritoneum, pleura, or pericardium. The rationale for this approach is based on the fact that clearance from a body cavity is delayed compared to clearance from the systemic circulation, resulting in a more prolonged exposure to higher regional concentrations of active agents. However, penetration of peritoneal tumor nodules by passive diffusion is limited by fibrotic adhesions, tumor encapsulations, and high interstitial pressures as a consequence of intratumoral capillary leak without functional lymphatic drainage. Therefore, it has been postulated that the major role for intracavitary chemotherapy administration would be in patients with minimal residual disease.

Cisplatin is well absorbed from the peritoneum into the bloodstream and has received the greatest attention for intraperitoneal delivery in ovarian cancer, achieving a laparotomy-confirmed response rate of greater than 32%. In view of the risk of systemic toxicity from cisplatin, there has been renewed interest in the use of intraperitoneal carboplatin, which differs in terms of protein binding and overall time required for activation.

In contrast to cisplatin, paclitaxel is poorly absorbed from the peritoneal compartment, suggesting that patients might benefit from combined intravenous and intraperitoneal administration to optimize tumor drug exposure. As a single agent, intraperitoneal paclitaxel demonstrated a 61% pathology-confirmed complete response rate among 28 assessable patients with initial microscopic disease. However, only 1 of 31 patients (3%) with greater than microscopic disease achieved a complete response.

Some agents, such as cyclophosphamide and ifosfamide, are prodrugs and must undergo irreversible metabolism to the active form, most commonly in the liver. For these agents, intraperitoneal administration would be ineffective, as it would achieve high local concentrations of the native compound, but without an opportunity for bioconversion.

Renal Excretion

The inactivation and excretion of chemotherapeutic agents occur primarily by the liver, kidneys, and body tissues, with lesser elimination through the stool. Table 1.1 lists drugs that require modification in the setting of renal or hepatic dysfunction.

Acute or chronic renal insufficiency is common in gynecologic cancer patients due to tumor-mediated obstruction, drug-induced toxicity, or advanced age. The incidence of moderate renal insufficiency dramatically increases with advancing age. For example, in the 60- to 69-year age group,

TABLE 1.1**MODIFICATIONS IN THE SETTING OF RENAL AND HEPATIC DYSFUNCTION**

Agents That Should Be Considered for Modification in the Presence of Moderate to Severe Renal Dysfunction	Agents That Generally Do Not Require Modification in the Presence of Moderate Renal Dysfunction	Agents That Should Be Considered for Modification in the Presence of Hepatic Dysfunction
Actinomycin D	Anastrozole	Docetaxel
Bleomycin	Bevacizumab	Doxorubicin
Capecitabine	Cetuximab	Epirubicin
Carboplatin	Docetaxel	Mitoxantrone
Cisplatin ^a	Doxorubicin	NAB-paclitaxel
Cyclophosphamide	Epirubicin	Paclitaxel
Etoposide	Erlotinib	PEG-liposomal doxorubicin
Ifosfamide	Fluorouracil	Vinblastine
Irinotecan	Gefitinib	Vincristine
Methotrexate	Gemcitabine	Vinorelbine
Topotecan	Letrozole	
	Leucovorin	
	Leuporelin	
	Megestrol	
	NAB-paclitaxel	
	Paclitaxel	
	Oxaliplatin	
	PEG-liposomal doxorubicin	
	Tamoxifen	
	Trastuzumab	
	Vinblastine	
	Vincristine	
	Vinorelbine	

^aCan be administered at full doses in anephric patients receiving hemodialysis.

over one third of women have an estimated glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m² (Fig. 1.1). In addition, serum creatinine levels can be inappropriately low as a consequence of reduced muscle mass, malnutrition, or alterations in fluid balance, and any of the standard formulae will overestimate GFR, with potential clinical consequences for drugs such as carboplatin, where dosing is based on renal clearance.

Several methods are available to estimate GFR (Table 1.2). All of these formulae are based on stable normalized biologic parameters and are less useful in the setting of dynamic changes following acute renal injury or nonrenal fluctuations in serum creatinine and fluid status, such as those that

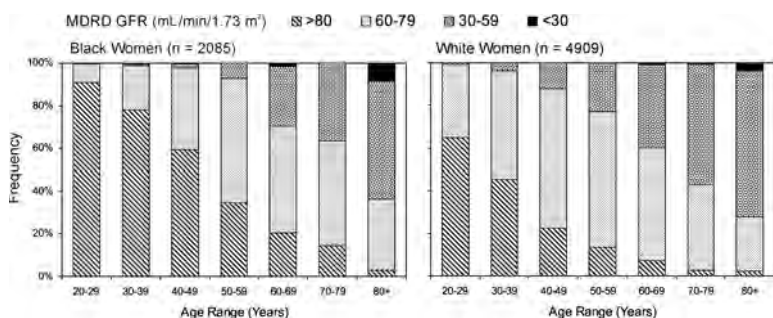


FIGURE 1.1. Distribution of renal function in nondiabetic adults. Weighted distribution of predicted GFR (mL/min/1.73 m²) based on the MDRD formula from the Third National Health and Nutrition Examination Survey (NHANES III).

might occur in the postoperative setting or in the presence of large-volume ascites or in patients with abnormal muscle mass. While urine collection for the measurement of creatinine clearance might be thought to provide a better estimate of GFR, it is also subject to great variability in clinical practice. The use of ⁵¹Cr-ethylenediaminetetraacetic acid (EDTA) clearance remains the standard for the measurement of GFR, but it is rarely used in clinical practice due to the cost and complexity associated with radioisotopes.

Metabolism and Pharmacogenomics

With the expanded knowledge of metabolic pathways and awareness of polymorphisms in key enzymes, it is sometimes possible to identify individuals with a dramatic increased risk of toxicity. For example, dihydropyrimidine dehydrogenase (DPD) controls the rate-limiting step in fluoropyrimidine metabolism, and approximately ten variant DPD alleles can occur with sufficient frequency to merit consideration of screening, as patients with less active DPD can be at risk for life-threatening mucosal injury and bone marrow suppression after receiving a single standard dose of 5-fluorouracil. While methods are available for screening, current assays can be expensive, and the potential reduction in risk needs to be balanced against the costs of a widespread screening program.

Uridine diphospho-glucuronosyl-transferase 1A1 (UGT1A1) is responsible for the glucuronidation of bilirubin and a number of drug metabolites, most notably SN-38, the major active metabolite of irinotecan. Patients with a deficiency in UGT1A1 are at increased risk for life-threatening diarrhea and bone marrow suppression after receiving irinotecan. While the UGT1A1*28 promoter mutation has been studied most extensively, mutations in the coding region can also occur, particularly in Asian populations, and may predict for efficacy in addition to toxicity. Gilbert syndrome is associated with a mild unconjugated hyperbilirubinemia and reduced activity of UGT1A1 that is also associated with an increased risk of toxicity in both homozygous and heterozygous patients.

TABLE 1.2

COMMONLY UTILIZED FORMULAE TO ESTIMATE CREATININE CLEARANCE (CRCL)

Formula Name	Estimation of CrCl
Cockcroft–Gault formula	$\text{CrCl (mL/min)} = (140 - \text{age}) \times \text{weight (kg)} \times (0.85 \text{ if female}) / \text{serum Cr (mg/dL)} \times 72$
Jelliffe formula	$\text{CrCl (mL/min)} = \{98 - [0.8 \times (\text{age} - 20)]\} \times (0.9 \text{ if female}) / \text{serum Cr (mg/dL)}$
MDRD formula	$\text{GFR [mL/min/1.73 m}^2\text{]} = 170 \times [\text{Serum Cr (mg/dL)}]^{-0.999} \times (\text{age})^{-0.176} \times (0.762 \text{ if female}) \times (1.180 \text{ if African American}) \times [\text{SUN (mg/dL)}]^{-0.170} \times [\text{Alb (g/dL)}]^{0.318}$

Alb, serum albumin concentration; BSA, body surface area; Cr, creatinine; GFR, glomerular filtration rate; MDRD formula, the Modification of Diet in Renal Disease study equation; SUN, serum urea nitrogen concentration.

Drug Interactions

During routine care, patients may receive a variety of drugs, including antiemetics, antihistamines (H1 and H2), steroids, nonsteroidal anti-inflammatory agents, anticoagulants, narcotics, and anti-infective agents. Table 1.3 summarizes some important drug interactions that may occur. Particular attention should be placed on drugs that could alter renal function, such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory agents, and diuretics in patients with reduced fluid intake.

Increased attention has been focused on drug metabolism and potential interactions at the level of CYP isozymes, particularly CYP-3A4, which is potentially linked to the metabolism of nearly half of all pharmaceutical agents. Drugs that are *substrates* for the same isozyme may competitively inhibit metabolism, but these interactions are usually not of clinical consequence. Drugs that *directly inhibit* CYP isozymes without being a substrate for that isozyme are more likely to have clinical consequences. These include itraconazole, ketoconazole, fluconazole, and erythromycin. Other drugs act as *inducers* of CYP isozymes by increasing gene expression or protein levels, such as glucocorticoids, barbiturates, and rifampin, which can increase the net activity of CYP-3A4, resulting in decreased concentrations of susceptible compounds. Among the anticancer agents that are substrates for CYP-3A4 are cyclophosphamide, ifosfamide, docetaxel, etoposide, paclitaxel (also CYP-2C8), vincristine, vinblastine, tamoxifen, and gefitinib.

Owing to the diversity and rapid adoption of new chemotherapy and nonchemotherapy compounds, information regarding drug interactions is best obtained from online databases (e.g., <http://www.medicalletter.com>, <http://www.micromedex.com>, or <http://www.druginteractioninfo.org/Home.aspx>) or the drug manufacturer.

TABLE 1.3**PHYSIOLOGIC AND PHARMACOLOGIC INTERACTIONS
IN CANCER CHEMOTHERAPY**

Interaction	Cause and/or Agent	Impact
Renal dysfunction	Obstruction, renal dysfunction, hypovolemia, hypotension, nonsteroidals, nephrotoxins (aminoglycosides, cisplatin)	Decreased clearance of methotrexate, carboplatin, and other agents
Hepatobiliary dysfunction	Biliary obstruction, hepatic dysfunction	Decreased clearance of doxorubicin, mitoxantrone, vincristine, vinblastine, etoposide, paclitaxel, and docetaxel
	Gilbert syndrome, glucuronidation polymorphisms (UGT1A1)	Increased exposure to SN-38 (irinotecan)
Microsomal activation	Hepatic dysfunction	Impaired activation of cyclophosphamide and ifosfamide
Altered protein binding	Carrier displacement (sulfonamides, salicylates, phenytoin)	Increased toxicity and higher free drug levels (methotrexate)
	Reduced carrier proteins (malnutrition)	Increased toxicity and higher free drug levels (cisplatin, paclitaxel, docetaxel, etoposide, and SN-38)
Altered intestinal absorption	Oral antibiotics (neomycin)	Decreased absorption of methotrexate
	High-fat meal	Increased bioavailability (lapatinib) Decreased bioavailability (capecitabine)
	Grapefruit juice (intestinal CYP-3A4 inhibition)	Increased bioavailability (cyclosporine, erythromycin, and benzodiazepines)
Decreased metabolism	Allopurinol	Delayed clearance (6-mercaptopurine)

Interaction	Cause and/or Agent	Impact
Decreased metabolism (<i>cont'd</i>)	DPD deficiency	Lethal toxicity (5-fluorouracil)
Cholinesterase inhibition	Cyclophosphamide, glucocorticoids	Decreased clearance (succinylcholine)
Monoamine oxidase inhibition	Procarbazine	Neurotoxicity and seizures (tricyclic antidepressants and phenothiazines)
MDR-1 competition	Natural products and other substrates, including verapamil, cyclosporine, tamoxifen	Decreased efflux and increased toxicity from natural products (doxorubicin, vincristine, paclitaxel, and docetaxel)
CYP-2C9	Inhibition	Capecitabine
	Induction	Glucocorticoids, barbiturates, rifampin
CYP-3A4	Inhibition	Ketoconazole, itraconazole, fluconazole, erythromycin
	Substrate competition	Cyclophosphamide, ifosfamide, paclitaxel, docetaxel, etoposide, vincristine, vinblastine, tamoxifen, gefitinib

GENERAL PRINCIPLES OF CHEMOTHERAPY

KEY POINTS

- *Dose intensity* refers to the total amount of drug administered over time. Increasing the dose intensity of paclitaxel and platinum agents above standard levels has not improved outcomes in ovarian cancer.
- *Dose density* refers to a shorter cycle interval. An increase in the dose density of paclitaxel has been shown to improve outcomes in breast cancer and may be beneficial for women with ovarian cancer.
- Combination therapy may improve response rates compared to sequential single therapy but often does not improve quality of life or overall survival.

Dose Intensity and Density

Dose intensity is a standardized measure of the amount of drug administered over time, most commonly expressed as mg/m²/week. Preclinical studies demonstrate a sigmoidal relationship between dose and tumor response. The hypothesis that greater dose intensity would produce greater benefit has been extensively evaluated in the setting of advanced ovarian cancer, beginning with a series of retrospective studies suggesting a correlation between actual delivered dose intensity and clinical outcomes. However, within practical dose ranges that can be achieved in the clinical setting, prospective randomized trials have not demonstrated significant improvements in either disease-free or overall survival. These frontline studies focused on platinum dose intensity. The question of paclitaxel dose intensity was also addressed in the setting of recurrent disease, again without any evidence of improved outcomes.

By contrast, there is a renewed interest in “dose-dense” therapy, in which agents are sequentially administered at maximal tolerated doses using short cycle intervals. This approach has been favorably evaluated in the adjuvant therapy of breast cancer, although it has not been clearly established if the clinical benefit is secondary to dose density or weekly scheduling of specific components.

Combination Versus Sequential Single-Agent Therapy

None of the standard combinations for advanced ovarian, endometrial, or cervical cancer have been directly compared to sequential therapy with the best active single agents, and the superiority of combination therapy has not been fully established. In the setting of ovarian cancer, Phase III trials have suggested that sequential therapy with platinum followed by paclitaxel may offer similar long-term outcomes to a combination of platinum and paclitaxel. Although the initial frequency of tumor response is often increased with combination therapy, long-term outcomes such as overall survival and symptom-adjusted quality of life can be similar for patients who receive optimal sequential therapy with single agents.

Chemotherapy Settings

Adjuvant chemotherapy refers to the initial use of systemic chemotherapy after surgery and/or radiation therapy has been performed with curative intent, and there is no evidence of residual disease. Adjuvant chemotherapy is considered if the subsequent risk for recurrence after initial definitive therapy is relatively high (generally >20%), but it is not routinely recommended when the risk of recurrence is less than 10%.

Concurrent chemotherapy with radiation (chemoradiation) refers to the use of chemotherapy to sensitize tumors to the effects of radiation generally delivered with curative intent. This has been most extensively studied in the primary management of locally advanced cervical cancer, where platinum-based chemoradiation has been proven to be superior to radiation alone.

Neoadjuvant chemotherapy generally refers to the use of chemotherapy in the management of locally advanced disease in situations where it would be difficult or impractical to perform immediate surgery or radiation. Following a response to initial chemotherapy, there is an expectation that morbidity associated with the overall treatment program can be minimized in conjunction with a reduction in the radiation treatment volume or the extent of surgery. This approach has been considered in advanced cervical cancer, where high initial response rates to neoadjuvant therapy have been observed. However, the long-term benefit of this approach has not been established. Neoadjuvant therapy is also a consideration in advanced ovarian cancer, particularly in patients with large-volume ascites, pleural effusions, diffuse small-volume disease, or comorbidities that might increase surgical risk.

Monitoring of Tumor Response

Generally accepted criteria for the evaluation of response are necessary to facilitate treatment decisions and comparisons among different regimens. The Response Evaluation Criteria in Solid Tumors (RECIST) are the most commonly used criteria in current clinical trials. RECIST is based on the prospective designation of at least one “target lesion” that measures at least 2 cm in one dimension, as well as “nontarget lesions” that are used to corroborate response (Table 1.4).

The summary response designation within RECIST integrates the findings from target and nontarget lesions, as well as serum tumor markers (if applicable). Serum tumor markers are not sufficient to declare response, but, if initially elevated, must normalize to designate a complete response. In the case of ovarian cancer, international criteria to declare disease progression on the basis of a serial elevation in CA-125 have been widely adopted, but there is incomplete agreement on criteria to define a partial response during treatment.

TABLE 1.4
OVERALL DISEASE RESPONSE CATEGORIES (RECIST)

Complete response (CR) ^a	Disappearance of all <i>target</i> ^b and <i>nontarget</i> lesions, and normalization of tumor marker levels (if appropriate)
Partial response (PR)	At least a 30% decrease in the sum longest diameter (LD) of <i>target</i> lesions (taking as reference the baseline sum LD) without the progression of <i>nontarget</i> lesions or the appearance of new lesions. <i>Note:</i> In the case where the only <i>target</i> lesion is a solitary pelvic mass measured by a physical examination (not radiographically measurable), a 50% decrease in the LD is required.

(continued)

TABLE 1.4

OVERALL DISEASE RESPONSE CATEGORIES (RECIST) (*continued*)

Progressive disease (PD)	At least a 20% increase in the sum LD of <i>target</i> lesions, taking as reference the smallest sum LD recorded since the start of the treatment, or the appearance of one or more new lesions, or the progression of any <i>nontarget</i> lesion. <i>Note:</i> In the case where the only <i>target</i> lesion is a solitary pelvic mass measured by a physical examination (not radiographically measurable), a 50% increase in the LD is required.
Stable disease (SD) ^c	Neither sufficient shrinkage of <i>target</i> lesions to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the start of the treatment. No appearance of new lesions (<i>target</i> or <i>nontarget</i>).

^aTo be assigned PR or CR, changes in tumor measurements must be confirmed by repeat assessments no less than 4 weeks after the criteria for response are first met. The duration of overall response is measured from the time that criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

^bAll measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as *target* lesions and recorded and measured at baseline. *Target* lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). All other lesions (or sites of disease) should be identified as *nontarget* lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each lesion should be noted throughout follow-up.

^cIn the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) that is defined in the study protocol. SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Measurable lesions—lesions that can be accurately measured in at least one dimension with LD ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Nonmeasurable lesions—all other lesions, including small lesions (LD < 20 mm with conventional techniques or < 10 mm with spiral CT scan), that is, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

MANAGEMENT OF TOXICITY

KEY POINTS

- Bone marrow toxicity is the most common serious toxicity of chemotherapy.
- Erythropoiesis-stimulating agents (ESA), such as erythropoietin, have been associated with decreased survival in randomized trials.

- Effective antiemesis therapy is critical and should be tailored to the emetogenic potential of the regimen.
- Carboplatin hypersensitivity reactions typically occur with the second dose of the second course of therapy, and may be severe.

Toxicity Assessment, Dose Modification, and Supportive Care

Chemotherapeutic regimens are universally toxic, with a narrow margin of safety. Initial chemotherapy dosing is based on body surface area, weight, renal function, and hepatic function, using guidelines from clinical trials. However, patient tolerance of treatment varies widely, and it is necessary to monitor toxicity with ongoing modifications to avoid serious acute and cumulative side effects.

The Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute has developed a detailed and comprehensive set of guidelines for the description and grading of acute and chronic organ-specific toxicities. The current version of the Common Terminology Criteria for Adverse Events (CTCAE) is available in electronic format from CTEP (<http://ctep.info.nih.gov>). Basic hematologic parameters are summarized in Table 1.5.

One convenient method of structured dose modification is illustrated in Table 1.6. With this approach, modifications for the subsequent course of therapy are implemented according to the degree (grade), duration, and timing of toxicity experienced during the preceding course. Although treatment can be delayed on a week-by-week basis to allow for recovery, delays of greater than 2 weeks should be avoided through dose modification and utilization of hematopoietic growth factors.

TABLE 1.5

CTCAE GRADING OF MYELOSUPPRESSION

Element	Grade			
	1	2	3	4
Leukocytes (per mm ³)	LLN to 3,000	<3,000 to 2,000	<2,000 to 1,000	<1,000
Granulocytes (per mm ³)	LLN to 1,500	<1,500 to 1,000	<1,000 to 500	<500
Hemoglobin (g/dL)	LLN to 10.0	<10.0 to 8.0	<8.0 to 6.5	<6.5
Platelets (per mm ³)	LLN to 75,000	<75,000 to 50,000	<50,000 to 25,000	<25,000

LLN, lower limit normal (institutional); CTCAE, Common Terminology Criteria for Adverse Events, version 3.0, Cancer Therapy Evaluation Program, National Cancer Institute, 10-JUN-2003 (<http://ctep.info.nih.gov/reporting/ctc.html>).

TABLE 1.6

REPRESENTATIVE DRUG DOSE MODIFICATIONS

Category (Timing)	Parameters	CTCAE Grade	Dose or Schedule Modifications
Granulocytes (day of therapy)	$>1,500/\text{mm}^3$	0 and 1	Full doses of all drugs.
	$<1,500/\text{mm}^3$	2, 3, and 4	Delay until recovered. If already delayed, reduce the dose by one level or add G-CSF.
Platelets (day of therapy)	WNL	0	Full doses of all drugs.
	$<\text{LLN to } 75,000/\text{mm}^3$	1	Delay until recovered.
	$<75,000/\text{mm}^3$	2	Delay until recovered. If already delayed, reduce the dose by one level.
Granulocytes (cycle nadir)	$>1,000/\text{mm}^3$	0, 1, and 2	Full doses of all drugs.
	$<500/\text{mm}^3$ for ≥ 7 days	4	Reduce the dose by one level. If already reduced, add G-CSF.
	$<1,000/\text{mm}^3$ with fever	3 and 4	Reduce the dose by one level. If already reduced, add G-CSF.
Platelets (cycle nadir)	$\geq 50,000/\text{mm}^3$	3	Full doses of all drugs.
	$<50,000/\text{mm}^3$ with bleed	3 and 4	Reduce doses by one level.
	$<25,000/\text{mm}^3$	4	Reduce doses by one level.

CTCAE, common toxicity criteria for adverse events; G-CSF, granulocyte colony-stimulating factor; LLN, lower limit normal; WNL, within normal limits.

Bone Marrow Toxicity

Bone marrow toxicity is the most common dose-limiting side effect associated with cytotoxic drugs, and neutropenia is the most common manifestation of bone marrow toxicity, occurring 7 to 14 days after the initial drug treatment and persisting for 3 to 10 days. For purposes of dose modification, the absolute neutrophil count (ANC) is preferred to total white blood count. Dose-limiting thrombocytopenia is less common than neutropenia, but it may be problematic with carboplatin.

Radiation, alkylating agents (e.g., melphalan and carboplatin), and other DNA-damaging agents (e.g., nitrosoureas and mitomycin C) can have cumulative long-term effects on the bone marrow. Most other agents, including the taxanes and topotecan, show no evidence of cumulative toxicity and can be administered for multiple cycles without any dose modification.

In view of the frequent occurrence of neutropenia and the risk of infectious complications, utilization of granulocyte colony-stimulating factors (G-CSF), including filgrastim or the longer-acting polyethylene glycol (PEG)-filgrastim, has increased. Although these agents promote more rapid granulocyte recovery, avoiding potential complications and facilitating the maintenance of dose intensity, their use has not been shown to improve long-term survival for patients with gynecologic cancer, compared to conservative management with dose reduction and cycle delay. In addition, G-CSF is not effective in the management of thrombocytopenia and may actually increase the degree of thrombocytopenia by the diversion of immature marrow elements.

Moderate degrees of anemia are quite common in cancer patients receiving chemotherapy, which may contribute to chronic fatigue. Erythropoiesis-stimulating agents (ESA), including erythropoietin (epoetin alfa) and darbepoetin, can ameliorate the anemia associated with chemotherapy, but there has been concern about data with regard to the potential risks associated with ESA, including cardiovascular events, thrombosis, and reduced tumor-related survival in placebo-controlled randomized trials. A Medicare decision memo limits reimbursement to patients with confirmed hemoglobin of less than 10 g/dL. In addition, these agents should not be used in patients being treated with curative intent.

Gastrointestinal Toxicity

There are three major categories of nausea and vomiting: *anticipatory*, occurring prior to the actual administration of chemotherapy; *acute onset*, beginning within 1 hour of chemotherapy administration and persisting for less than 24 hours; and *delayed*, beginning more than 1 day after chemotherapy administration and persisting for several days.

The antiemetic regimen is tailored to the emetogenic potential of the treatment, which reflects the incorporation of specific drugs, as well as the dose and schedule of drug administration. Table 1.7 categorizes chemotherapy agents according to their emetic potential. Mild nausea and vomiting can often be managed effectively with H-1 antihistamines (diphenhydramine), phenothiazines (prochlorperazine or thiethylperazine), steroids

TABLE 1.7

EMETOGENIC POTENTIAL OF ANTINEOPLASTIC AGENTS
(NCCN PRACTICE GUIDELINES)

Level	Agent
High emetic risk (>90% frequency of emesis) ^a	• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide • Altretamine • Carmustine > 250 mg/m² • Cisplatin ≥ 50 mg/m² • Cyclophosphamide > 1,500 mg/m² • Dacarbazine • Mechlorethamine • Procarbazine (oral) • Streptozocin
Moderate emetic risk (30%–90% frequency of emesis) ^a	• Aldesleukin > 12–15 million units/m² • Amifostine > 300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan > 4 mg/d • Carboplatin • Carmustine ≤ 250 mg/m² • Cisplatin < 50 mg/m² • Cyclophosphamide ≤ 1,500 mg/m² • Cyclophosphamide (oral) • Cytarabine > 1 g/m² • Dactinomycin • Daunorubicin • Doxorubicin • Epirubicin • Etoposide (oral) • Idarubicin • Ifosfamide • Imatinib (oral)^b • Irinotecan • Lomustine • Melphalan > 50 mg/m² • Methotrexate ≥ 250 mg/m² • Oxaliplatin > 75 mg/m² • Temozolomide (oral) • Vinorelbine (oral)
Low emetic risk (10%–30% frequency of emesis) ^a	• Amifostine ≤ 300 mg • Bexarotene • Capecitabine • Cytarabine (low dose) 100–200 mg/m² • Docetaxel • Doxorubicin (liposomal) • Etoposide • Fludarabine (oral)

Level	Agent
	• 5-Fluorouracil • Gemcitabine • Ixabepilone • Methotrexate > 50 mg/m² < 250 mg/m² • Mitomycin • Mitoxantrone • Nilotinib • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Topotecan • Vorinostat
Minimal emetic risk (<10% frequency of emesis) ^a	• Alemtuzumab • Alpha interferon • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Busulfan • Cetuximab • Chlorambucil (oral) • Cladribine (2-chlorodeoxyadenosine) • Decitabine • Denileukin diftitox • Dasatinib • Dexrazoxane • Erlotinib • Fludarabine • Gefitinib • Gemtuzumab ozogamicin • Hydroxyurea (oral) • Lapatinib • Lenalidomide • Melphalan (oral low dose) • Methotrexate ≤ 50 mg/m² • Nelarabine • Panitumumab • Pentostatin • Rituximab • Sorafenib • Sunitinib • Temsirolimus • Thalidomide • Thioguanine (oral) • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vinorelbine

^aProportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

^bDaily use of antiemetics is not recommended based on clinical experience.

(dexamethasone or methylprednisolone), benzamides (metoclopramide), or benzodiazepines (lorazepam). For drugs with more severe emetogenic potential, a 5-hydroxytryptamine (5-HT₃) receptor antagonist, such as ondansetron or granisetron, should be given prior to chemotherapy and repeated at 8- to 12-hour intervals. This may be combined with dexamethasone or the neurokinin-1 receptor antagonist, aprepitant. Longer acting 5-HT₃ antagonists have also become available, including palonosetron and dolasetron, which require only a single dose prior to chemotherapy. Anticipatory nausea and vomiting can become a significant problem during repeated cycles of chemotherapy and can sometimes be modulated by pretreatment with benzodiazepines, such as lorazepam. Unfortunately, this particular schedule produces significant sedation and can be used only in hospitalized patients or outpatients with independent transportation.

Diarrhea, oral stomatitis, esophagitis, and gastroenteritis are also potential problems. Patients with significant oral or esophagogastric symptoms may have their symptoms managed with oral viscous lidocaine (2%), other topical anesthetics, or parenteral narcotics in severe cases. Randomized controlled trials have demonstrated that multiple intravenous doses of recombinant keratinocyte growth factor (palifermin) before and after treatment can reduce the incidence and severity of chemotherapy-induced oral stomatitis associated with bolus 5-fluorouracil or high-dose chemotherapy. In general, dose-limiting mucosal injury is uncommon with platinum-based combinations, taxanes, and other single agents used in the treatment of gynecologic cancer.

Alopecia

Scalp alopecia is one of the most emotionally taxing side effects of chemotherapy. Aside from long-lasting alopecia that follows cranial irradiation, it is almost always reversible, but it can be a major deterrent to successful chemotherapy. A variety of physical techniques have been devised to minimize alopecia, including scalp tourniquets and ice caps designed to decrease scalp blood flow. Although partially effective, they are rarely successful with extended chemotherapy.

Skin Toxicity

Skin toxicities that occur during chemotherapy include allergic or hypersensitivity reactions (HSRs), skin hyperpigmentation, photosensitivity, radiation recall reactions, nail abnormalities, folliculitis, palmar-plantar erythrodysesthesia (PPE, hand-foot syndrome), and local extravasation necrosis.

PPE is a reversible but painful erythema, scaling, swelling, or ulceration involving the hands and feet. This occurs more often with chronic oral or intravenous medications, weekly treatment regimens, and formulations that increase drug circulation time, such as prolonged oral etoposide, weekly and continuous-infusion 5-fluorouracil, capecitabine, and PEG-liposomal doxorubicin, where it has emerged as a major dose-limiting toxicity.

Extravasation necrosis is a serious complication seen after tissue infiltration of vesicant drugs such as doxorubicin, dactinomycin, mitomycin C, and vincristine. Any suspected infiltration should prompt immediate removal of the intravenous line and application of ice packs to the infiltrated area every 6 hours for 3 days. Small series have reported a limited experience with local infiltration or topical application of steroids, *n*-acetylcysteine, dimethyl sulfoxide, and hyaluronidase with variable results, and recommendations are imprecise. However, single or multiple intravenous doses of dexrazoxane, a topoisomerase II catalytic inhibitor, appear to offer specific protection against injury from anthracyclines, including doxorubicin and daunorubicin. Skin necrosis from some extravasations may eventually require surgical debridement and skin grafting.

Neurotoxicity

Peripheral neuropathy is the most common neurotoxicity encountered in gynecologic oncology and is a particular risk with the administration of cisplatin and paclitaxel. Although less common with carboplatin than cisplatin, neuropathy can still occur, particularly in combination with paclitaxel. Peripheral neuropathy generally begins with symptoms of paresthesia (numbness and tingling) accompanied by a loss of vibratory and position sense in longer nerves associated with the feet and hands. It then progresses to functional impairment, with gait unsteadiness and loss of fine motor coordination, such as trouble buttoning clothes and writing. In moderate cases with paclitaxel and other nonplatinum agents, this is almost always reversible but may require several months post-therapy for substantial improvement. In more severe cases, symptoms may persist for the lifetime of the patient. If related to cisplatin, neuropathy can continue to progress after therapy has been discontinued, with long-term persistence of symptoms. Cisplatin has also been associated with permanent ototoxicity and, at higher doses, with a loss of color vision and autonomic neuropathy.

Patients with underlying neurologic problems, such as diabetes, alcoholism, or carpal tunnel syndrome, are particularly susceptible to neurotoxicity, and substitution of docetaxel for paclitaxel can be a useful strategy in some situations. All patients who receive potentially neurotoxic therapy should be routinely queried regarding symptoms so that severe damage can be avoided.

There has been an interest in agents that might prevent nerve damage, encourage recovery, or ameliorate symptoms. However, thus far, small studies with glutamine, vitamin E, and other agents have been inconclusive. Amifostine appears to be of borderline effectiveness, and there are no agents that can be recommended for the prevention of neuropathy in routine practice. Clinical management of painful paresthesias has been reported with amitriptyline and gabapentin.

Other neurotoxicities include acute and chronic encephalopathies, usually associated with intrathecal chemotherapy. Of particular relevance to the gynecologic cancer population, an acute reversible metabolic

encephalopathy has been well described in association with ifosfamide and attributed to the toxic metabolite chloroacetaldehyde. This syndrome can potentially be prevented or treated by infusion of methylene blue, which may act through inhibition of monoamine oxidase activity with reduced chloroacetaldehyde formation in the liver.

Genitourinary Toxicity

Renal toxicity is a well-recognized side effect of cisplatin, even though only a small fraction of cisplatin is cleared by renal excretion. By contrast, carboplatin undergoes extensive renal clearance with little risk of toxicity. Careful attention to hydration status and saline-driven urinary output before, during, and immediately after cisplatin therapy is required to reduce the risk of renal failure.

Hemorrhagic cystitis can be seen with cyclophosphamide or ifosfamide, attributed to the metabolite acrolein. With moderate-dose cyclophosphamide, this complication can be prevented by maintaining a high urinary output, which reduces the overall urothelial exposure to the toxic metabolites. The risk of cystitis is essentially 100% with ifosfamide unless there is simultaneous administration of mesna, which binds and neutralizes acrolein in the urine.

Hypersensitivity Reactions

Paclitaxel is formulated in Cremophor-EL, a mixture of polyoxyethylated castor oil and dehydrated alcohol, which has been associated with mast cell degranulation and clinical HSR. Over 80% of reactions to paclitaxel occur within minutes during either the first or the second cycle of drug administration and can usually be managed with prophylactic medication (corticosteroids, histamine H1/H2 blockade, etc.) followed by rechallenge beginning at a lower rate of infusion. Similar reactions have been reported with docetaxel and PEG-liposomal doxorubicin, which are not formulated in Cremophor-EL, but their frequency is lower. Emerging data with NAB-paclitaxel indicate a marked reduction in the risk of HSR.

With improved survival and an increased utilization of second-line therapy, patients can also experience more traditional allergic reactions to selected chemotherapy agents. Carboplatin, an organoplatinum compound, has emerged as a major source of late allergic reactions. These occur most often during the second cycle of a second course of therapy, suggesting a process of antigen recall and priming of the immune response. Patients receiving the second course of carboplatin-based therapy should be closely monitored for early signs of hypersensitivity to avoid more serious reactions. Unlike the situation with paclitaxel, carboplatin reactions are not readily prevented or circumvented with prophylactic medication, although inpatient and outpatient strategies for desensitization have been reported and successfully utilized for patients who are responding to re-treatment. However, the desensitization routine must generally be repeated with each cycle of treatment.

Other Significant Toxicities

These include cardiac toxicity from cumulative doxorubicin exposure, radiation recall vasculitis from doxorubicin, pulmonary fibrosis from bleomycin, gonadal dysfunction in premenopausal women from alkylating agents, and secondary acute leukemia from the chronic administration of alkylating agents, particularly melphalan in ovarian cancer.

Suggested Readings

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CHAPTER 2 ■ BIOLOGIC AND PHYSICAL ASPECTS OF RADIATION ONCOLOGY

INTRODUCTION TO RADIOBIOLOGY

KEY POINTS

- A typical course of radiation therapy is given in 10 to 40 fractions administered over 2 to 8 weeks, with each fraction killing a percentage of cells.
- Radiation exerts most of its deleterious effects by creating free radicals that cause breaks in two opposing strands of DNA.
- Oxygen chemically modifies radiation-induced DNA damage making it irreparable.
- Hypoxia, conversely, shifts the cell survival curve to the right.
- Both the total dose of radiation and how fast it is delivered affect outcomes.
- Cell sensitivity to radiation varies in different phases of the cell cycle with late S-phase being most radioresistant and M-phase being most radiosensitive.

Radiobiology is the study of the action of ionizing radiations on living things. The size and histology of the tumor, as well as the relationship of the tumor to the normal organs within the radiation field, help determine the total dose and the dose per fraction.

Tumor Control Probability and Cell Survival Curves

Radiation effects exhibit a sigmoidal dose response curve. The following is a theoretical dose-response curve for tumor control probability and normal tissue complications in the presence and absence of chemotherapy (Fig. 2.1). Ideally, there is a great deal of separation between the curve on the left, representing chances of tumor control, and the curve on the right, representing the chance for toxicity.

A typical course of radiation therapy is given in 10 to 40 fractions administered over 2 to 8 weeks. Each fraction kills a fixed percentage of cells. The log cell kill model describes cell kill in very simplistic terms such that a given radiation dose will kill a certain percentage of cells and that a tumor receiving a fractionated course of radiation gets progressively smaller with time. Additionally, tumor cells may have undergone clonogenic cell death wherein they are still present but unable to reproduce.

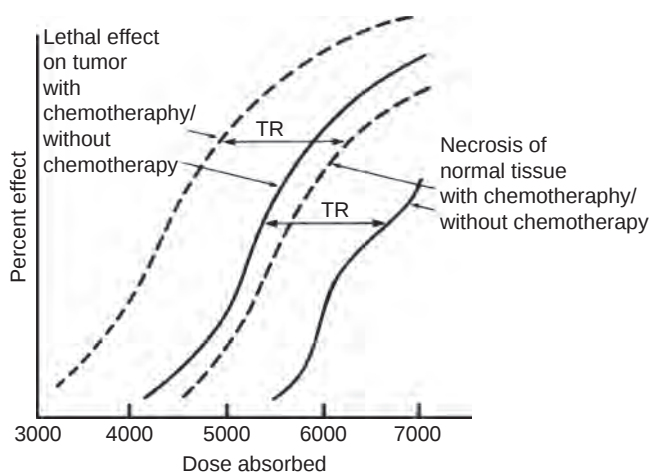


FIGURE 2.1. Theoretic curves for tumor control and complications as a function of radiation dose both with and without chemotherapy. TR, therapeutic range, or the difference between tumor control and complication frequency.

Source: Reprinted from Perez CA, Thomas PRM. Radiation therapy: Basic concepts and clinical implications. In: Sutow WW, Fernbach DJ, Vietti TJ, eds. *Clinical Pediatric Oncology*. 3rd Ed. St. Louis, MO: Mosby; 1984:167, with permission from Elsevier.

Therefore, one does not necessarily have to kill all cancer cells in order to achieve cure if the remaining ones are unable to reproduce.

The shape of the cell survival curve is best described by the linear-quadratic model with DNA as the lethal target. Radiation exerts most of its deleterious effects by causing breaks in two opposing single strands in the DNA backbone. Attempted repair of a double stranded break may result in two possible outcomes: Lethal outcomes and nonlethal outcomes. Nonlethal repair may result in a reciprocal translocation and preservation of the genetic information. In some instances, the reciprocal translocation results in the activation of an oncogene, which may manifest as a malignancy.

DNA Damage Repair and the Shape of Cell Survival Curves

The concept that DNA damage repair drives the shapes of cell survival curves is well illustrated by experiments showing the effectiveness of oxygen as a sensitizer. Oxygen is known to chemically modify radiation-induced DNA damage, making it irreparable. This is known as the oxygen fixation hypothesis. Therefore, under anoxic conditions, DNA damage repair would be expected to increase considerably. Hypoxia causes the cell survival curve to shift to the right and change shape.

Biologically Equivalent Dose

Both the total dose of radiation and how fast it is delivered can produce very different outcomes. The same holds true for fractionated courses of radiation. The linear quadratic equation can be used to derive an equation to be used as a guide to predict various biologic endpoints and is given by the following equation:

$$\text{BED} = D[1 + d/(\alpha/\beta)]$$

BED is the biologically equivalent dose, D is total dose, d is dose per fraction, α/β is dose where the alpha component of cell kill equals the beta component.

The Cell Cycle

The cell cycle is an ordered set of events, resulting in cell growth and division into two daughter cells. The steps are G1-S-G2-M. The G1 stands for “GAP 1” and S-phase stands for “Synthesis” and is the point at which DNA replication occurs. Late S-phase is the most radioresistant phase of the cell cycle since the DNA repair machinery for replication also can repair radiation damage. The G2 stage stands for “GAP 2” and M-phase stands for “mitosis” and is when nuclear division occurs. M-phase is also the most radiosensitive phase of the cell cycle. Any DNA damage caused generally will be passed along to the daughter cells and may be fatal. This is one important reason why rapidly dividing cells such as cancers are radio-sensitive. G0 is a stable state of the cell and is typically observed with well-differentiated cells that have reached the end stage of development and are no longer dividing (i.e., neuron).

INTRODUCTION TO RADIATION PHYSICS

KEY POINTS

- The most common forms of radiation used in therapy are photons (X- and γ -rays) and electrons.
- There is an increased penetration as the energy of X- or γ -rays is increased.
- X- and γ -rays differ in their source of production: X-rays are artificially produced whereas γ -rays arise through the natural process of radioactive decay within the nucleus of an atom.
- Exposure is the amount of ionization produced in air by photons, and its unit is roentgen (R).
- Radiation deposits energy in tissue by transferring energy from photons to ionized particles, which in turn transfer energy to the medium (usually tissue).
- The SI unit for absorbed dose is also joule per kilogram or Gray, which has replaced the previously used term “rad.” 1 Gray = 100 cGy = 100 rads.

Radiation physics is the study of the interaction of radiation with matter. In the treatment of patients with radiation, this matter is either tumor tissue or normal tissues.

Units Used in Radiation and Radiation Therapy

Radiation is an abbreviation for electromagnetic radiation. It can occur in numerous forms. The most common forms used in radiation therapy are X-rays, γ -rays, and electrons. X- and γ -rays are also known as photons. Electrons are a form of particle beam radiation. Other particles or forms of radiation include protons, neutrons, and heavier alpha particles.

X- and γ -rays are forms of electromagnetic radiation, similar to visible light, but with a much smaller wavelength, that is, greater energy. The difference between X- and γ -rays is only their respective origins. Modern radiotherapy treatment machines termed linear accelerators or linacs create X-rays artificially by bombarding an atom or tungsten target with high-speed electrons. Linacs can produce both photon and electron beams of different energies depending on their construction. There is an increased penetration as the energy of X- or γ -rays is increased. The X-rays produced by linacs are much more penetrating than Cobalt (^{60}Co) γ -rays.

While X-rays are artificially produced, γ -rays arise through the natural process of radioactive decay within the nucleus of an atom. These radioactive isotopes can occur naturally or be created artificially. Examples include the brachytherapy sources Cesium (^{137}Cs) and Iridium (^{192}Ir) as well as Cobalt (^{60}Co) teletherapy treatment machines. Table 2.1 lists many of the more common radioactive isotopes and their physical properties. For gynecologic cancers, use of Radium 226 (^{226}Ra) sources is now historic.

Electrons are negatively charged particles and will usually only penetrate a few millimeters to centimeters in tissue. Similar to photons, the higher the energy of the electron, the farther it will penetrate into the tissue. Electrons are used to treat tumors or tissues close to the skin surface such as superficial inguinal nodes and tumors of the skin, including vulvar cancers.

Regarding photon interactions with tissue, the dominant process at megavoltage (MV) energies used in radiation therapy is termed the Compton effect.

Table 2.2 lists some basic units of radiation and radiation therapy, both in historic context and in terms of modern SI units. Exposure is the amount of ionization produced in air by photons, and its unit is the Roentgen (R). The SI unit for exposure is coulomb per kilogram (C/kg) with $1 \text{ R} = 2.58 \times 10^{-4} \text{ C/kg air}$. Kerma (Kinetic Energy Release per unit Mass) defines the transfer of energy from photons to directly ionized particles. These directly ionized particles, in turn, transfer some of their energy to the medium (usually tissue). This transfer of energy is defined as the absorbed dose to the medium from the radiation beam. The SI unit for kerma is joule per kilogram (J/kg) or Gray (Gy). The SI unit for absorbed dose is also joule per kilogram or Gray, which has replaced the previously used term “rad.” Often times the term centigray (cGy) is used. The cGy is equivalent to the rad and 1 Gray equals 100 cGy.

TABLE 2.1

PHYSICAL PROPERTIES AND USES OF BRACHYTHERAPY RADIONUCLIDES

Element	Isotope	Energy (MeV)	Half-life	HVL-Lead (mm)	Source Form	Clinical Application
OBSOLETE SEALED SOURCES OF HISTORIC SIGNIFICANCE						
Radium	²²⁶ Ra	0.83 (avg)	1,626 years	16	Radium salt encapsulated in tubes and needles	LDR intracavitary and interstitial
Radon	²²² Rn	0.83 (avg)	3.83 days	16	Radon	Permanent interstitial Temporary molds
CURRENTLY USED SEALED SOURCES						
Cesium	¹³⁷ Cs	0.662	30 years	6.5	Cesium salt encapsulated in tubes and needles	LDR intracavitary and interstitial
Iridium	¹⁹² Ir	0.397 (avg)	74 days	6	Seeds in nylon ribbon Encapsulated source on steel cable	LDR temporary interstitial HDR interstitial and intracavitary
Cobalt	⁶⁰ Co	1.25	5.26 years	11	Encapsulated spheres	HDR intracavitary
Iodine	¹²⁵ I	0.028	59.6 days	0.025	Seeds	Permanent interstitial
Palladium	¹⁰³ Pd	0.020	17 days	0.013	Seeds	Permanent interstitial
Gold	¹⁹⁸ Au	0.412	2.7 days	6	Seeds	Permanent interstitial
Strontium	⁹⁰ Sr- ⁹⁰ Y	2.24 MeV $\beta_{\max}$	28.9 years		Plaque	Superficial ocular lesions

(continued)

TABLE 2.1
PHYSICAL PROPERTIES AND USES OF BRACHYTHERAPY RADIONUCLIDES (continued)

Element	Isotope	Energy (MeV)	Half-life	HVL-Lead (mm)	Source Form	Clinical Application
DEVELOPMENTAL SEALED SOURCES						
Americium	²⁴¹ Am	0.060	432 years	0.12	Tubes	LDR intracavitary
Ytterbium	¹⁶⁹ Yb	0.093	32 days	0.48	Seeds	LDR temporary interstitial
Californium	²⁵² Cf	2.4 (avg) neutrons	2.65 years			
Samarium	¹⁴⁵ Sm	0.043	340 days	0.060	Seeds	LDR temporary interstitial
UNSEALED RADIOISOTOPES USED FOR RADIOPHARMACEUTICAL THERAPY						
Strontium	⁸⁹ Sr	1.4 MeV $\beta_{\max}$	51 days		SrCl ₂ IV solution	Diffuse bone metastases
Iodine	¹³¹ I	0.61 MeV $\beta_{\max}$ 0.364 MeV γ	8.06 days		Capsule NaI oral solution	Thyroid cancer
Phosphorus	³² P	1.71 MeV $\beta_{\max}$	14.3 days		Chronic phosphate colloid instillation Na ₂ PO ₃ solution	Ovarian cancer seeding; peritoneal surface polycythemia vera, chronic leukemia

TABLE 2.2

SI UNITS FOR RADIATION THERAPY

Quantity	SI Unit (Special Name)	Non-SI Unit	Conversion Factor
Exposure	C kg ⁻¹	roentgen (R)	1 C kg ⁻¹ ≈ 3,876 R
Absorbed dose, kerma	J kg ⁻¹ (gray [Gy])	rad	1 Gy = 100 rad
Dose equivalent	J kg ⁻¹ (sievert [Sv])	rem	1 Sv = 100 rem
Activity	s ⁻¹ (becquerel [Bq])	curie	1 Bq = 2.7 × 10 ⁻¹¹ Ci

RADIATION PRODUCTION

KEY POINTS

- Intensity modulated radiation therapy (IMTR) is accomplished by using small computer-controlled leaves in the head of the machine (multileaf collimators or MLCs) to block the beam in different patterns, modulating beam intensity and creating multiple complex treatment fields. The result is improved target coverage and increased sparing of normal tissues.
- Image guided radiotherapy refers to the imaging of treatment fields prior to treatment delivery in order to precisely align patient and improve treatment accuracy.

Radioactive Isotopes

As mentioned before, γ -rays are typically derived from radioactive isotopes, for example, ^{60}Co . Electrons or beta particles also come from radioactive isotopes. Radioactivity is the result of an atom changing its “energy” state, usually to a lower “energy” state, by the emission/absorption/internal conversion of photons or electrons in the atom.

Radioactivity, or activity, is denoted by the symbol A and is defined as the number of disintegrations per unit of time. The equation describing radioactive decay is $A = A_0 e^{-\lambda t}$, where A_0 is the initial activity, λ is the decay constant, and t is some unit of time later. Other important units for radioactivity and radioactive decay are the half-life ($T_{1/2}$) and the average life (T_a). The half-life is the amount of time necessary to reduce the original amount of material by half. $T_{1/2}$ is related to the decay constant by $T_{1/2} = 0.693/\lambda$. T_a is related to the decay constant and the half-life by $T_a = 1/\lambda = 1.44 T_{1/2}$.

Cesium 137 (^{137}Cs) has replaced radium as a safer, equally effective radioisotope. It is typically used for low dose rate (LDR) gynecologic brachytherapy in tandem and ovoid and cylinder applicators. Iridium 192 (^{192}Ir)

comes in various activities and can be used for interstitial and intracavitary gynecologic implants.

Linear Accelerators

Linacs produce radiation by accelerating an initial beam of electrons across a variable electric field. This electron beam can be adjusted to control its shape and intensity before delivery to the patient. Alternatively, the electron beam can be directed to a tungsten target. The electron-target interaction creates a forward scattered photon beam or X-ray. The

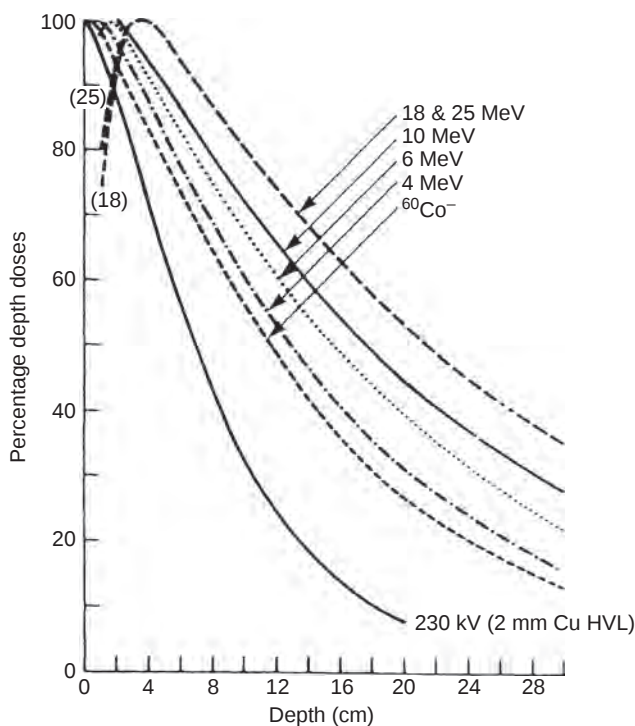


FIGURE 2.2. Typical X-ray or photon beam central-axis percentage depth-dose curves for a 10×10 cm beam for 230 kV (2 mm Cu HVL) at 50 cm SSD, ^{60}Co and 4 MV at 80 cm SSD, and 6, 10, 18, and 25 MV at 100 cm SSD. The last two beams coincide at most depths but do not coincide in the first few millimeters of the build-up region. The 4-, 6-, 18-, and 25-MV data are for the Varian Clinic 4, 6, 20, and 35 U, respectively, at the Department of Radiation Oncology, Washington University in St. Louis. HVL, half value layer; SSD, source to skin distance.

Source: From Cohen M, Jones DEA, Greene D. Central axis depth dose data for use in radiotherapy. *Br J Radiol.* 1972;11:21, with permission.

resulting photon beam can then be modified by the machine using filters and collimators to produce the desired radiation field shape.

Photon beams of different energies have a different absorbed dose pattern within tissues. This pattern is normally characterized as a percent depth dose or variation of dose as a function of depth within tissue, as shown in Figure 2.2. The higher energy photons deposit dose at greater depths, and less dose is deposited at shallow depths. This is called “skin sparing” and is a characteristic of high-energy photons.

Modern linacs come equipped with MLCs and asymmetric jaws to control the shape of the radiation beam directed before it reaches the patient. MLCs are small (projected size at the patient approximately 1 cm) adjustable collimators built into the linac gantry that work together to create a shaped opening mimicking the effects of a poured block. With the advent of computer-controlled motion of the MLCs, the radiation field can be controlled to produce an intensity-modulated radiation therapy (IMRT) treatment. In IMRT treatments, the MLCs are used to create many small fields of radiation within a larger treatment field. This adaptability allows the radiation treatment planner to create and deliver very complex treatment fields that improve target coverage while attempting to spare normal tissues. IMRT treatment plans are an improvement of the more conventional three-dimensional conformal treatment plans. IMRT is being explored for the treatment of gynecologic cancers. RTOG 0418 has defined parameters for contouring of targets and normal organs, margin size, and dose volume constraints in the postoperative setting in early cervical or endometrial cancers. An online atlas has been developed to improve consistency between multiple contouring physicians.

A relatively new feature for radiotherapy treatments is image-guided radiation therapy (IGRT). Modern linacs have added on board imaging that allows the treatment fields to be recorded electronically at every treatment setup using an electronic portal imaging device. By comparing computer-generated radiographs (DRRs or digitally reconstructed radiographs) with the actual patient images, discrepancies in field shape and patient setup can be corrected before the delivered treatment. This type of corrective behavior before treatment is the foundation of IGRT. The latest variation on IGRT is the addition of computed tomography (CT) scanners within the linac to verify more completely the correct alignment of the patient on the treatment table prior to treatment.

Simulation

The conventional simulator uses a diagnostic (kV) photon beam to reproduce all the gantry, collimator, and table rotations used in a linac treatment, and therefore “simulates” the actual treatment. CT-based simulators (“CTSim’s”) have largely replaced conventional simulators and combine a diagnostic CT scanner with a software package that allows for the simulation of the necessary gantry angles and table angles modeled in the computer. Following the scan, the treatment isocenter and the full CT images are transferred to the computer planning system for further treatment planning. DRRs of the treatment field are created for later comparison to actual treatment images.

Computerized Dosimetry

In a modern radiotherapy department, computers are necessary to accurately calculate the absorbed doses to tissues. These absorbed doses within tissues are termed isodoses, or lines of the same dose. To initiate this process, CT images are acquired of the area of interest at a pretreatment planning session or simulation. These scans are typically obtained on the CT simulator. Treatment targets such as pelvic lymph nodes, the uterus, or vagina are identified through contouring on these images, as are normal tissues such as the rectosigmoid, bladder, and small bowel. Dose goals are identified for the targets and normal tissues. A dosimetrist uses this information to design the radiation treatment plan, which is reviewed by the treating physician and a physicist and is altered as needed to best address the tumor and avoid the normal organs and tissues.

The goal for most treatment plans is to treat the target to a specified dose while minimizing dose to adjacent normal tissues. Figure 2.3 illustrates the gross target volume (GTV), the clinical target volume (CTV), the planning target volume (PTV), and the treated volume. The CTV includes all of the GTV plus possible microscopic extensions. The PTV includes all of the CTV plus a margin to account for possible geometric uncertainties of the patient or treatment margin. The irradiated volume includes all of the PTV plus any margins that might be included in the treatment plan to provide minimum dose coverage to the PTV.

DEFINITION OF "VOLUMES" IN RADIATION THERAPY

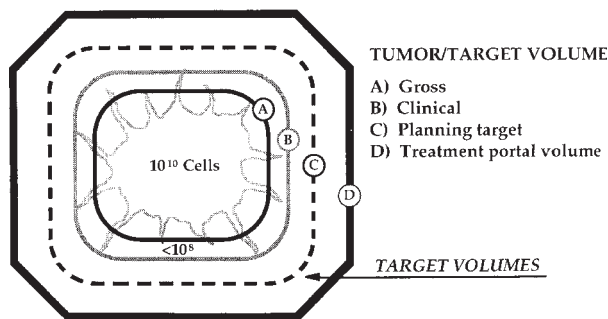


FIGURE 2.3. Schematic representation of “volumes” in radiation therapy. The treatment portal volume includes the GTV, potential areas of local and regional microscopic disease around the tumor (clinical), and a margin of surrounding normal tissue (planning).

Source: From Perez CA, Purdy, JA. Rationale for treatment planning in radiation therapy. In: Levitt SH, Khan FM, Potish RA, eds. *Levitt and Tapley's Technological Basis of Radiation Therapy: Practical and Clinical Applications*. 2nd Ed. Philadelphia, PA: Lea & Febiger; 1992. Modified in Perez CA, Brady LW, Roti JL. Overview. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd Ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:1, with permission.

BRACHYTHERAPY PRINCIPLES

KEY POINTS

- Brachytherapy delivers a concentrated dose of radiation to immediately adjacent tissues by implanting radioactive sources within a patient.
- Implants can be temporary or permanent.
- In gynecologic malignancies, temporary implants are used most frequently and are categorized as interstitial (sources are directly inserted into tumor-bearing tissues) or intracavitary (sources are placed into naturally occurring body cavities or orifices such as the vagina or uterus).
- Dose rate is the amount of dose delivered over an interval of time. Low dose rate is defined as 40 to 100 cGy per hour. High dose rate is defined as 20 to 250 cGy per minute.

Brachytherapy is a term with Greek roots where “brachy” means “short distance.” With brachytherapy, a highly concentrated dose of radiation is delivered to immediately surrounding tissues within millimeters to several centimeters of the applicators that carry the radioactive sources. This allows for a high dose of radiation to be delivered to closely approximated tumor and to relatively spare surrounding normal tissues such as the rectosigmoid, bladder and small bowel.

There are different types of brachytherapy or radioactive implants. Temporary implants are used most frequently and are categorized as interstitial or intracavitary. With interstitial brachytherapy, the radioactive sources are transiently inserted into tumor-bearing tissues directly through placement in hollow needles or tubes. With intracavitary brachytherapy, radioactive sources are placed into naturally occurring body cavities or orifices such as the vagina or uterus using commercially available hollow applicators such as a vaginal cylinder or tandem and ovoids. Permanent interstitial implants entail the insertion of radioactive seeds (Iodine 125 [^{125}I]; Gold 198 [^{198}Au]; Palladium 103 [^{103}Pd]) directly into tumor-bearing tissues to emit radiation continuously as they decay to a nonradioactive form.

Dose rate is also an important variable in brachytherapy. Traditional LDR irradiation has been used for decades in gynecologic cancers using ^{226}Ra and ^{137}Cs sources for intracavitary insertions and low activity ^{192}Ir sources for interstitial insertions. High dose rate (HDR) brachytherapy has gradually been introduced over the last several decades and entails the use of a highly radioactive (^{10}Ci) ^{192}Ir source. Standard ranges for LDR are 40 to 100 cGy per hour and for HDR, 20 to 250 cGy per minute that is 1,200 to 15,000 cGy per hour. Pulsed dose rate uses a medium strength ^{192}Ir source of 0.5 to 1.0 Ci with dose rates of up to 3 Gy per hour, and delivers the treatment in a “pulsed” method over only 10 to 30 minutes of each hour as opposed to LDR techniques, which deliver 30 to 100 cGy per hour continuously over several days. PDR delivers the same total dose over the same total time at the same hourly rate as LDR, but with an instantaneous dose rate higher than LDR, and was developed to combine the isodose optimization of HDR brachytherapy with the biologic advantages of LDR.

The term “afterloading,” refers to an unloaded applicator that has radioactive sources introduced after insertion. Nearly all modern brachytherapy exploits afterloading. Remote afterloading, which eliminates all personnel exposure, entails the use of a computer-driven machine to insert and retract the source(s), which are attached to a cable.

CLINICAL APPLICATIONS

KEY POINTS

- The Manchester system approach for prescribing brachytherapy dose relied on predetermined doses and dose rates directed to fixed points in the pelvis.
- “Point A” was defined as 2 cm lateral to the central canal of the uterus and 2 cm from the mucous membrane of the lateral fornix in the axis of the uterus.
- Standard definitive total doses to points A and B when combined with external beam therapy at a dose rate of 50 to 60 cGy per hour are 85 and 60 Gy, respectively.
- Upper limit of total doses to normal tissue from combined external beam and brachytherapy are as follows: Bladder more than 75 to 80 Gy; rectum less than 70 to 75 Gy; vaginal surface: 120 to 140 Gy.
- Patterns of Care Studies have revealed that brachytherapy is the single most important treatment factor in multivariate analysis for stage III-B cervix cancer with respect to survival and pelvic control.

Brachytherapy Systems for the Treatment of Cervical Cancer

Intracavitary brachytherapy for cervical carcinoma was profoundly impacted by the development of various “systems” that attempted to combine empiricism with a more scientific and systematic approach. Three systems developed in Europe, including the Paris System, the Stockholm system, and the Manchester System. The Manchester system principles are an integral part of modern brachytherapy.

The Manchester System

The Manchester system standardized treatment with predetermined doses and dose rates directed to fixed points in the pelvis. The fixed points A and B were selected on the theory that the dose in the paracervical triangle impacted normal tissue tolerance rather than the actual doses to the bladder, rectum, and vagina. “Point A” was defined as 2 cm lateral to the central canal of the uterus and 2 cm from the mucous membrane

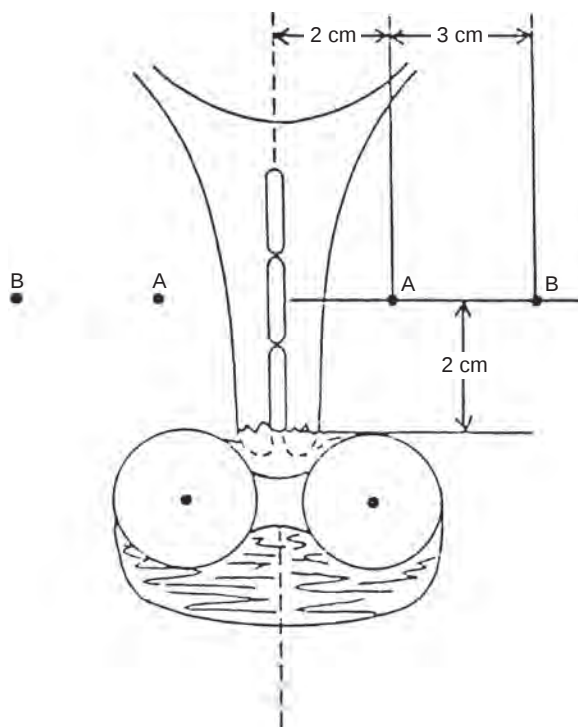


FIGURE 2.4. The Manchester system. Definitions of points A and B in the classical Manchester system are found in the text. In a typical application, the loading of intrauterine applicators varied between 20 and 35 mg of radium and between 15 and 25 mg of radium for each vaginal ovoid. The resultant treatment time to get 8,000 R at point A was 140 hours.

Source: From Meredith WJ. *Radium Dosage: The Manchester System*. Edinburgh: Livingstone; 1967, with permission.

of the lateral fornix in the axis of the uterus (Fig. 2.4). It often correlates anatomically with the point of crossage of the ureter and uterine artery and was taken as an average point from which to assess dose in the paracervical region. “Point B” was located 5 cm from midline at the level of point A and was thought to correspond to the location of the obturator lymph nodes. To achieve consistent dose rates, a set of strict rules dictating the relationship, position, and activity of radium sources in the uterine and vaginal applicators was devised. With current LDR applications using Cesium rather than radium, it is considered standard to have a point A dose rate of 50 to 60 cGy per hour and to deliver a total dose of 85 Gy to point A and 60 Gy to point B when combined with external beam therapy.

The Fletcher (M.D. Anderson) System

The Fletcher system was established at M.D. Anderson Hospital in the 1940s. The Fletcher applicator was subsequently developed and remains an integral part of gynecologic brachytherapy. The primary prescription parameter in the Fletcher system was tumor volume and prescription rules were based on maximum mg-hours and maximum time, taking into account the total external beam dose and the calculated sigmoid dose. Standardized source arrangements and limits on the vaginal surface dose and mg-hours were all used to help specify treatment. Individualization to fit the anatomical situation was an essential aspect of this system.

The Fletcher colpostats were a further evolution of the Manchester ovoids and were made with the same diameters of 2, 2.5, and 3 cm but were more cylindrical than Manchester “ovoids” and were attached to handles, with shielding in the direction of the bladder and rectum. Later models were afterloading and loaded with ^{137}Cs instead of ^{226}Ra . Recommended loadings were 15, 20, and 25 mg of radium for the 2, 2.5, and 3 cm colpostats, respectively, and 5 to 10 mg for the mini-ovoids. Recommended tandem loadings were usually 15–10–10 mg of radium with the amount of radium in the tandem usually greater than that in the ovoids.

The current M.D. Anderson approach to treatment specification reflects a policy of treating advanced cervical carcinoma to normal tissue tolerance. This includes integrating standard loadings and mg-hours with calculated doses to the bladder, rectum, sigmoid, and vaginal surface. The activity in the ovoids is limited by the vaginal surface dose, which is kept below 140 Gy. Calculated bladder and rectal doses are noted and are sometimes used to limit the duration of the intracavitary system, with the combined external beam and implant doses for the bladder kept at less than 75 to 80 Gy and for the rectum at less than 70 to 75 Gy. Mg-Ra-eq hours are usually limited to 6,000 to 6,500 after 40 to 45 Gy external beam. In a recent retrospective review of cervical cancer patients treated definitively at M.D. Anderson, the median total dose to point A from external beam and intracavitary irradiation was 87 Gy and the median doses to the bladder and rectum were 68 and 70 Gy. The total dose delivered to the vaginal surface was limited to 120 to 140 Gy or 1.4 to 2.0 times the point A dose. These total doses to point A and the vagina, bladder, and rectum are used as contemporary guidelines for determining implant duration and therefore dose.

Dose Specification Points for Cervical Cancer

Most institutions use a derivation of the Manchester (point A) or Fletcher systems (mg-hours combined with qualitative assessment of implant geometry) to specify dose and implant duration, and though variations exist, most will attempt to quantify doses in the paracervical region (point A), and at either point B or the pelvic wall (C or E), and the rectum and bladder. MRI-based brachytherapy is under investigation to assess and modify the dose to the actual tumor volume rather than relying on point A alone.

Importance of Brachytherapy in Cervical Cancer

When curative treatment is planned, patients with cervical carcinoma treated with definitive irradiation should receive a combination of external beam irradiation and brachytherapy. As revealed in the Patterns of Care Studies (PCS) and the retrospective series of Perez et al., recurrences and complications are decreased when brachytherapy is used in addition to external beam. Use of an intracavitary implant was the single most important treatment factor in multivariate analysis for stage III-B cervix cancer with respect to survival and pelvic control in the 1973 and 1978 PCS. Retrospective series with external beam alone have proven marginal outcomes with this approach.

INTRACAVITARY APPLICATORS: CERVICAL CANCER

Low Dose Rate

The best-known LDR applicators are the Fletcher-Suit and Henschke tandem and ovoid (colpostat) applicators. In the 1970s, the Delclos mini-ovoid was developed for use in narrow vaginal vaults. The mini-ovoids do not have shielding added inside the colpostat, and this together with their smaller diameter produces a higher surface dose than regular ovoids with resultant higher doses to the rectum and bladder.

The Fletcher-Suit-Delclos tandem and cylinder applicator was designed to accommodate narrow vaginas where ovoids may be contraindicated and to treat varying lengths of the vagina when mandated by vaginal spread of disease. The cylinders vary in size from 2 to 5 cm to accommodate varying vaginal sizes. Vaginal cylinders increase the length of vagina and rectum treated with an associated increase in complications including vaginal fistulae, rectal ulcers, and strictures. Interstitial implantation should also be a consideration for patients with a narrow vagina or with distal vaginal disease.

Interstitial Applicators: Cervical and Vaginal Cancers—LDR and HDR

Interstitial implantation is appropriate in select patients with bulky tumors, anatomical distortion such as an obliterated endocervical canal or narrow vagina, or recurrent disease. The development of prefabricated perineal templates, through which stainless steel needles were inserted and after-loaded with ^{192}Ir or ^{125}I , was pivotal in advancing interstitial techniques for the treatment of cervical and vaginal cancers. The Syed-Neblett (Best Industries, Springfield, VA) is one well-known commercially available template system. Typically, total LDR doses to the tumor volume or reference isodose from the implant range from 23 to 40 Gy over 2 to 4 days.

The total HDR dose will be approximately 60% of the total LDR dose and will be given in divided fractions.

External whole pelvic irradiation (39.6 to 45.0 Gy) generally precedes implantation. The total LDR dose to the reference volume from the combined implant and external beam approximates 70 to 85 Gy over 8 weeks.

High Dose Rate Brachytherapy for Cervical Cancer

Though LDR techniques have been the traditional standard for decades for gynecologic brachytherapy, HDR techniques have gained increased acceptance and use more recently due to some inherent advantages.

HDR advantages are the following:

1. Outpatient therapy
2. Reproducibility: The shortened treatment time provides a greater degree of certainty that applicator displacement as a function of time will be decreased.
3. Dosimetric advantages: The newer systems, which allow a single source to “dwell” at a site for a calculated period of time, combined with dose optimization software programs, provide a significant further improvement in the ability to shape the dose distribution.
4. Improved dose distributions may allow for a reduction in normal tissues doses.
5. Potential reduction in treatment duration: Integration of HDR one to two times per week with external beam irradiation three to four times per week can lead to a shorter overall treatment duration, which may be pivotal in maximizing cure.
6. Decreased exposure to health care providers with the use of remote afterloading systems.
7. Potential radiobiologic advantages: Reoxygenation of hypoxic cells can take place between fractions and this may in fact be a radiobiologic advantage of HDR.

HDR disadvantages are the following:

1. Lower therapeutic ratio: HDR lowers the therapeutic ratio compared to LDR, and there is a potential increase in late tissue effects with large fraction sizes.
2. Labor intensity: There is an increase in the number of implants per patient from 1–3 to 3–6 (range, 2 to 16).
3. The need for sedation may still exclude high-risk patients even though bed rest is not required.

Conversion from LDR to HDR

A basic concept is that the total dose with HDR must be less than with LDR and the number of fractions must increase (70 to 74). This concept comes from early radiobiologic studies, and calculations have shown that one must give approximately 60% of the LDR dose with HDR.

High Dose Rate Applicators

The tandems and ovoids used with HDR are variations of the traditional Fletcher and Henschke LDR applicators but are lighter, narrower, and smaller. The ovoids are 2.0, 2.5, and 3.0 cm in diameter with and without shielding.

The ring applicator, which is an adaptation of the Stockholm technique, has become a popular applicator. The ring applicator is ideal for patients without lateral vaginal fornices. Its ease of insertion and predictable geometry make it a popular alternative to tandem and ovoids.

Tandem and cylinder applicators are used in the setting of a narrow vagina or vaginal extension of disease and are available in diameters of 2.0 to 4.0 cm. As with LDR tandem and cylinder applicators, the bladder and rectal doses may increase with this applicator and the dose distribution will be more cylindrical than pear-shaped, which can underdose bulky tumors.

Dose-Fractionation Schemes

Different fractionation schedules have been reported for HDR brachytherapy, with the dose per fraction at point A varying from 3 to 10.5 Gy, the number of fractions from 2 to 13, and the number of fractions per week from 1 to 3. Currently the most common approach in the United States is to use five fractions of 5 to 6 Gy in combination with whole pelvis irradiation of 45 to 50 Gy.

Sequencing with External Beam

In nonbulky disease presentations, HDR insertions are often integrated early in the treatment course after approximately 20 Gy of external beam RT. Alternatively, some institutions choose to take the whole pelvis to 40 to 45 Gy initially, preceding the five HDR insertions, unless the patient has very early disease or evidence of early vaginal stenosis. Compressing the duration of treatment to less than 60 days may be desirable. HDR and external beam fractions should not be given on the same day.

Brachytherapy for Endometrial Cancer

Hysterectomy is the cornerstone of treatment for endometrial carcinoma. Selective use of vaginal brachytherapy, external beam irradiation or both in the postoperative setting is based on the histopathologic risk factors identified in the tissues removed at the time of surgical staging. Vaginal brachytherapy is typically performed using Fletcher colpostats, or a variety of vaginal cylinders (Delclos, Burnette). Both LDR and HDR techniques are used. Vaginal ovoids are available in diameters of 2 to 3 cm with associated caps and shielding and treat approximately the upper third of the vagina. Vaginal cylinders are available in diameters of 2 to 5 cm, with or without shielding, and can treat a portion of or the entire vagina. Distal vaginal recurrences or metastases are rare after radiation and occurred in

0.5% to 1% of patients when the upper vagina was treated. It is therefore not suggested to treat more than the upper half of the vagina routinely. Typically, the length of vagina treated with vaginal cylinders is between 4 and 5 cm, perhaps favoring a longer length when using brachytherapy alone. Due to the longer length of vagina treated and the lack of packing, a larger volume of rectum and bladder will be treated with cylinders.

Most vaginal brachytherapy for endometrial cancer is performed with vaginal cylinders using HDR techniques. The dose distribution should ideally conform to the shape of the cylinder, and dose is typically specified either at the vaginal applicator (mucosal surface) surface or at a depth of 0.5 cm from the applicator or vaginal mucosal surface. For LDR insertions, vaginal surface doses of 50 to 80 Gy are reported most frequently in the literature. When used with external beam, cumulative doses of 60 to 100 Gy at the vaginal surface are reported in the literature. For a vaginal recurrence of endometrial cancer, doses of 80 Gy and higher may be needed when combining external beam and brachytherapy.

Vaginal brachytherapy alone is generally considered an option for patients treated with hysterectomy, with either no or selective lymph node sampling, who are thought to be at low risk for lymph node metastases, or in the setting of a negative pelvic lymph node dissection, even when high risk factors such as high grade or deep myometrial invasion are present.

There is debate if a vaginal cuff boost is routinely necessary in addition to external beam irradiation for early-stage endometrial cancer, and there are little data to support it. Practice patterns are based more on institutional tradition and individual preference rather than prospective randomized trials; however, doses in excess of the 45 to 50 Gy typically delivered with external beam may be necessary if there are microscopic tumor cells embedded in the hypoxic vaginal cuff.

Medically inoperable endometrial cancer is an unusual situation in the current era. When encountered, it can require the use of sophisticated radiation techniques. Either external beam alone or brachytherapy alone may be appropriate for some patients or a combination of the two.

Patients with recurrent endometrial cancer usually benefit from both external beam and brachytherapy. Doses in excess of 80 Gy may lead to better local control in these patients. In patients with residual vaginal disease less than 0.5 cm in maximum thickness, vaginal cylinders or ovoids can be used whereas in patients with thicker lesions following external beam, interstitial techniques are needed.

EXTERNAL BEAM IRRADIATION FOR GYNECOLOGIC CANCERS

KEY POINTS

- In cervical and vaginal cancers, the role of external beam irradiation is to shrink bulky tumor to bring it within range of the high-dose portion of the intracavitary dose distribution and improve tumor geometry

by shrinking tumor that may distort anatomy and prevent optimal brachytherapy.

- In cervical, endometrial, and vaginal cancers, external beam additionally sterilizes paracentral and nodal disease.

Cervical and Vaginal Cancers

In cervical and vaginal cancers, the role of external beam irradiation is to shrink bulky tumor prior to implantation to bring it within range of the high-dose portion of the intracavitary dose distribution, improve tumor geometry by shrinking tumor that may distort anatomy and prevent optimal brachytherapy, and sterilize paracentral and nodal disease that lies beyond reach of the intracavitary system. For endometrial cancer, many of the same nodes are at risk as in cervical cancer, but the spread of disease is not as predictable with the paraaortic nodes independently at risk. The presacral nodes are also not at risk unless there is cervical involvement. Both the pelvic and paraaortic nodes are at risk in all sites of uterine involvement, and grade, myometrial invasion, and lymphatic vascular space invasion are more predictive of risk than location. For all gynecologic cancers, patterns of lymphatic spread influence the external beam field borders. For specifics on external beam doses and techniques, please refer to the respective chapters on cervical, endometrial, vulvar, and vaginal cancer.

Radiation-Induced Tissue Effects

The response of a tissue or organ to radiation depends on two factors: (a) the inherent sensitivity of the individual cells and (b) the kinetics of the population as a whole of which the cells are a part. These factors combine to account for the substantial variation in response to radiation characteristic of different tissues. Additionally, the volume of tissue irradiated as well as the dose, dose rate, and fractionation scheme will affect both acute and late toxicities. The addition of chemotherapy or other systemic agents may impact on toxicity as may other medical comorbidities such as diabetes, hypertension, collagen vascular diseases, Crohn's disease, and ulcerative colitis, as well as social risk factors such as smoking. The tolerance doses for tissues are described by the TD 5/5 or the probability of a 5% risk of complications within 5 years of the completion of radiation and TD 5/50 or the probability of a 50% risk of complications within 5 years.

Skin

When treating the vulvar and inguinal regions there can be marked skin reactions. Erythema is the first visible skin reaction and is usually seen about the third week of radiation. Other skin reactions include dry desquamation and moist desquamation occurring after the fourth week of radiation. Return of the epidermis can take 10 to 14 days. Late manifestations of radiation on the skin include depigmentation, subcutaneous fibrosis,

dryness and thinning with the loss of apocrine and sebaceous glands, thinning or loss of hair, and telangiectases. Necrosis of the skin is rare and generally occurs only with doses of radiation in excess of 60 Gy.

Vagina

There are few noticeable acute reactions when treating the upper two thirds of the vagina with radiation. Some patients may notice a white-yellow vaginal discharge, which is due to mucositis of the vaginal mucosa. This can be evident during radiation and continue for several months after radiation. The lower third of the vagina, however, is less tolerant of radiation than the proximal and the tolerance doses are in the range of 80 to 90 Gy versus 120 to 150 Gy, respectively. Vaginal narrowing and shortening is a late sequela of radiation, which can alter and impede sexual function. Combined brachytherapy and external beam irradiation will cause more late effects than either modality alone. The uterus is very resistant to high doses of radiation as is evident in patients treated with external beam and brachytherapy for cervical cancer. Rare cervical necrosis can occur.

Bladder/Ureters/Urethra

Acute and transient radiation cystitis may be observed with moderate doses of irradiation (>30 Gy). Patients will report urinary frequency and urgency as well as mild dysuria and decreased bladder capacity. Higher radiation doses may cause more severe symptoms of cystitis and spasms of the bladder musculature. It is important to rule out the presence of a concomitant bacterial infection. Radiation cystitis is characterized by the presence of white cells and red cells without bacteria on urinalysis.

Doses above 60 Gy can cause chronic cystitis, telangiectasias, hematuria, fibrosis, and decreased bladder capacity. Rarely, bladder neck contractures as well as fistulas may occur. Fistulas are more likely to occur if there is invasion of the bladder wall by tumor or in the setting of interstitial implants. Studies have demonstrated that with doses below 75 to 80 Gy to limited volumes of the bladder, the incidence of grade 3 or 4 complications is 5% or less, whereas with higher doses, a greater incidence of sequelae is noted. The ureters are quite resistant to radiation and rare ureteral stenosis is reported in some series. Interstitial implants are more likely to cause this than intracavitary, as can early placement of a narrow midline block. Urethral stenosis is also rare.

Small Intestine, Large Intestine, and Stomach

It is common to observe watery diarrhea with intermittent abdominal cramping starting in the second or third week of abdominal or pelvic irradiation. Increased peristalsis, disturbance of the absorption mechanisms, and a decreased transit time also occur. Patients will report increased flatulence and noisy bowel sounds. Rarely patients will report nausea.

Concurrent 5-fluorouracil (5-FU) or Gemcitabine can worsen small bowel toxicity. The late effects of radiation on the small bowel can be a continuation of the acute effects. Some patients will experience chronic diarrhea. Small bowel obstructions occur in approximately 5% of irradiated patients, and the ileum is the most common loop of bowel involved.

When the rectum is included in the irradiated volume, there is rectal discomfort with tenesmus, and mucus production, sometimes mixed with blood in the stools. Hemorrhoids may worsen during radiation. This constellation of symptoms is termed “proctitis.”

Late radiation effects with high enough doses include temporary or permanent ulceration and bleeding due to telangiectasias. Fibrosis, stenosis, perforation, and fistula formation are rarer. In general, doses in excess of 60 Gy are necessary to produce this more advanced radiation damage to the small bowel and rectosigmoid.

Acute effects involving the stomach, like the small and large bowel reactions, include erosions and thinning and subsequent edema and ulceration. Symptoms can include nausea, vomiting, reflux, and pain. Late effects can include gastritis and ulceration with associated bleeding. Progressive fibrosis can lead to gastric outlet obstruction and rarely perforation, all of which are dose and volume dependent.

Ovaries

In premenopausal patients treated with definitive irradiation, the ovaries will be irradiated incidentally and ovarian failure will occur. Hot flashes and other menopausal symptoms can begin to develop during radiation. Alternatively, the ovaries can also be elevated out of the radiation field and placed above the true pelvis to attempt to avoid them when treating cervical cancer. The dose necessary to castrate a woman depends on her age: A larger dose is required during the period of more active follicular proliferation. A single dose of 4.0 to 8.0 Gy or fractionated doses of 12 to 20 Gy (depending on age) are known to produce permanent castration and sterility in most patients.

Bone Marrow/Pelvic Bones

The lymphocytes are the most radiosensitive cells in the bone marrow. The rate of fall of the various components of the marrow is a function of the half-lives of the mature cells. These half-lives are as follows: erythrocyte—120 days, granulocytes—6.6 hours, platelets—8 to 10 days. Pelvic irradiation may cause transient lymphopenia. This is even more of an issue when whole abdominal or extended field irradiation is used due to the increased bone marrow in the radiation fields. Prior or concurrent chemotherapy will also lead to an increased bone marrow toxicity. The frequent monitoring of the CBC is considered standard of care with pelvic or abdominal irradiation.

Insufficiency fractures can also develop in irradiated pelvic bones. These most commonly involve the sacrum and ileum, followed by the

pubic bones, and rarely the acetabulum. MRI is the best imaging modality to detect them and also rule out recurrent disease. Symptoms from these changes in the pelvic bones will often improve over time, but patients may also suffer future symptoms from the exacerbation of these fractures or the development of new fractures over time. Femoral neck complications can include avascular necrosis as well as fracture. This is a rare complication following the irradiation of the inguinal nodes.

Liver

Veno-occlusive disease is the pathologic entity caused by radiation to the liver, resulting in necrosis and atrophy of the hepatic cells. During radiation, the liver enzymes may be elevated, and can continue following completion of radiation. Signs of radiation hepatitis can include a marked elevation of alkaline phosphatase (three to ten times normal) with much less elevation of the transaminases (normal to two times normal). The TD 5/5 for whole liver is 30 Gy. Small portions of the liver can receive up to 70 Gy.

Kidney

The kidneys are very sensitive to small doses of radiation, and a common goal is to avoid greater than 18 to 20 Gy whole kidney dose. When delivering whole abdominal or paraaortic irradiation, the kidneys are at risk and the equivalent of one kidney must be spared. Functional changes have been described after exposure of the kidney to more than 20 Gy and signs and symptoms of renal dysfunction can follow including hypertension, leg edema, and a urinalysis showing albuminuria and low specific gravity. A normocytic, normochromic anemia may also appear.

Doses to Bladder and Rectosigmoid—LDR

The bladder and rectosigmoid are the organs of concern in the setting of combined external beam irradiation and brachytherapy. Maximum bladder doses of 75 to 80 Gy and rectal doses of 70 to 75 Gy are guidelines. Small bowel doses should be limited to 45 to 50 Gy with 60 Gy maximum. The volume of rectum and bladder irradiated is an important variable in the development of complications in addition to the cumulative dose.

Doses to Bladder and Rectosigmoid—HDR

Rectal and sigmoid complications occur earlier than bladder complications. Rectal bleeding is the most frequent rectal morbidity occurring in approximately 30% of patients. Fowler has speculated that if only 80% of the tumor dose is received by the critical normal tissues, then four to six HDR fractions can be used safely.

When possible, the doses to the normal critical structures should be less than the dose at point A, perhaps in the range of 50% to 80%.

CT scanning after applicator placement is exceedingly helpful and much more reliable in assessing the proximity of the sigmoid to the tandem and in manipulating the dose distribution.

FUTURE FOCUS

Reduction of morbidity and improvement in local control and cure is a common goal in the treatment of patients with gynecologic cancers. Directly relating the intracavitary system to the anatomy through the use of CT and MRI seems to be the next step in the lineage of dosimetric systems. The GEC ESTRO Gyn Working Group has developed guidelines for defining and contouring tumor volumes and normal tissues on MRI scans with the brachytherapy applicators in place, and some data have shown a decrease in complications and an increase in local control with use of MRI-guided brachytherapy for cervical cancer.

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CHAPTER 3 ■ CLINICAL GENETICS OF GYNECOLOGIC CANCER

GENETICS IN CLINICAL PRACTICE OF GYNECOLOGY ONCOLOGY

The identification of BRCA1 in 1994 and BRCA2 in 1995 has introduced a new component to the practice of gynecologic oncology. Genetic testing for predisposition to ovarian cancer became available by 1996 and is now well established. There are five genes for ovarian cancer susceptibility now in clinical use (BRCA1, BRCA2, MLH1, MSH2, and MSH6). BRCA1 and BRCA2 are responsible for the hereditary breast-ovarian cancer syndrome (10% to 15% of all ovarian cancers) and MLH1, MSH2, and MSH6 are responsible for the hereditary nonpolyposis colon cancer syndrome (2% of ovarian cancers) (Tables 3.1 and 3.2). Current strategies for prevention include prophylactic surgery and chemoprevention with oral contraceptives. Screening for ovarian cancer is widespread, but its utility is unproven.

OVARIAN CANCER

KEY POINTS

- 10% to 15% of all ovarian cancer is associated with a BRCA1 or BRCA2 mutation.
- Prophylactic oophorectomy is an effective method of ovarian cancer risk reduction for mutation carriers.
- Ovarian cancer screening remains unproven.

Genetic Epidemiology

Approximately 10% to 15% of all women with invasive ovarian cancer carry a BRCA1 or BRCA2 mutation and several national groups suggest offering genetic testing to all woman diagnosed with invasive epithelial ovarian cancer (with the exception of mucinous cancers). In the event of a positive genetic test, testing is extended to unaffected female relatives. However, if there is no living affected relative, then testing may begin with an unaffected woman.

The frequency of BRCA mutations among ovarian cancer patients is not the same for all ethnic groups. In some populations, there are recurrent (founder) mutations. In these populations, the overall frequency of BRCA1 mutations tends to be high and a large proportion of mutations will be

TABLE 3.1
LIFETIME RISKS OF CANCERS ASSOCIATED WITH SPECIFIC GENES

	BRCA1	BRCA2	MMR ^a
Breast	50%–85%	50%–85%	NI
Ovarian	30%–40%	15%–25%	5%–10%
Endometrial	NI	NI	40%–60%

^aMismatch repair genes MSH2, MLH1, and MSH6.
NI, not increased.

accounted for by one, or a small number, of specific mutations. For example, approximately 30% to 40% of Jewish women with ovarian cancer carry one of the three founder mutations (two in BRCA1 and one in BRCA2). The frequency of BRCA mutations has been estimated at 1 in 12 cases of ovarian cancer in French-Canadians and 1 in 6 cases in Pakistan. In these populations, it may be possible to offer testing for a limited number of mutations. The excess risk of ovarian cancer in Jewish families with multiple cases of breast or ovarian cancer appears to be almost entirely due to the three Jewish founder mutations. Among women with a BRCA mutation, the ovarian cancer incidence is much greater than expected. If a founder mutation is not identified through screening of a Jewish family, it is exceedingly unlikely that a different mutation will be found. This also implies that a Jewish woman without one of the three mutations should not be considered to be at increased risk for ovarian cancer (although she may be at higher than average risk for breast cancer).

In the ethnically mixed populations of North America, approximately 13% of all patients with invasive ovarian cancer carry a mutation in BRCA1 or BRCA2. However, the range of mutations is wide and genetic testing must be comprehensive (full genomic screening). Among BRCA1 carriers, the risk of ovarian cancer is significant in women above the age of 35 (approximately 1% per year) and preventive measures must be initiated early. Women who carry a pathogenic mutation in the BRCA1 gene have a lifetime risk of approximately 40% for developing invasive ovarian cancer. Among BRCA2 carriers, the risk is lower and usually does not occur below age 50. A recent meta-analysis estimated the risk of ovarian cancer to be 16%. Also, among BRCA2 carriers, the risk of ovarian cancer varies with the position of the mutation.

Pathology and Surgical Presentation of Hereditary Ovarian Cancer

Ovarian cancers that occur in women with a BRCA mutation appear to be similar to their sporadic counterparts with the exception that mucinous tumors and tumors of low malignant potential (or “borderline” tumors)

TABLE 3.2

GENES ASSOCIATED WITH COMMON CANCERS

Breast	Ovary	Colon	Endometrial
BRCA1	BRCA1		
BRCA2	BRCA2	APC	
ATM	MSH2	MSH2	MSH2
CHEK2	MLH1	MLH1	MLH1
NBS1	MSH6	MSH6	MSH6
P53			PTEN

are rarely observed in women with a BRCA mutation. The great majority of BRCA-linked ovarian cancers show moderate to poor differentiation. Most hereditary ovarian tumors present at an advanced surgical stage but stage I or II tumors are now being discovered in the context of high-risk screening programs, or as an incidental finding associated with a prophylactic oophorectomy in an asymptomatic woman. Several studies have reported on the presence of early ovarian cancers among pathology specimens obtained at the time of prophylactic surgery. The frequency of occult malignancy ranges between 2% and 10%. Some of these early tumors are identified in the distal fallopian tube suggesting that this may be a site of origin for some of the ovarian/fallopian cancers in high-risk women. It is necessary that the fallopian tube be completely removed and serially sectioned when a prophylactic oophorectomy is performed.

Clinical Outcome and Treatment Effects

A number of studies have reported that the survival of patients with BRCA-associated ovarian cancer is improved, compared to women with sporadic ovarian cancer. A study of consecutive cases of ovarian cancers that compared BRCA-associated cancer to sporadic ovarian cancers from the same institution found that BRCA mutation status was a favorable and independent predictor of survival for women with advanced disease. It is not yet clear if the improved survival rate is the result of a difference in the natural history of ovarian cancer in the two subgroups, or is the result of a better response of BRCA-associated tumors to current therapies.

Prophylactic Oophorectomy

In 1995, a consensus panel of the NIH-recommended prophylactic oophorectomy for high-risk women at age 35 years, or after childbearing is complete. It seems logical that prophylactic oophorectomy should eliminate the incidence of ovarian cancer, but there are two reasons for the potential

failure of prophylactic oophorectomy. First, it is possible that the removed ovaries or fallopian tubes contain foci of occult carcinoma and that the cancer had spread locally to the peritoneum at the time of the resection. Secondly, it is possible that *de novo* cancer arises in the peritoneum after oophorectomy. The peritoneum is derived from coelomic epithelium, of the same embryologic origin as the surface epithelium of the ovary.

It is difficult to measure the risk of peritoneal cancer in women with intact ovaries. Peritoneal, fallopian and serous ovarian cancers are histologically indistinguishable and symptomatic women often present with multiple foci of cancer involving the peritoneum, tubes, omentum and ovary. Tubal cancer is also difficult to discriminate from ovarian cancer and may be classified as ovarian cancer. New serous cancers that arise in the abdominal peritoneum, following an oophorectomy, are considered to be primary peritoneal cancers.

Piver et al. reported that 6 of 324 women who underwent prophylactic oophorectomy experienced primary peritoneal cancer. The mutation status of these women was unknown and there was no standard period of follow-up. Kauff et al. followed 170 BRCA carriers for an average of 2 years. They observed 1 peritoneal cancer among 98 women who chose salpingo-oophorectomy, versus 5 ovarian/peritoneal cancers in 72 women with intact ovaries. In a historical cohort study of 551 BRCA1 and BRCA2 carriers, Rebbeck et al. reported that the incidence of ovarian or peritoneal cancer was diminished by 96% (95% confidence interval [CI]: 84% to 99%) in women who underwent prophylactic oophorectomy, compared to those with intact ovaries.

Finch et al. followed 1,045 women with a mutation who underwent a bilateral prophylactic salpingo-oophorectomy and compared the cancer risk with 783 women who did not undergo the procedure. The overall reduction in cancer risk associated with bilateral oophorectomy was 80% (hazard ratio = 0.20; 95% CI: 0.07 to 0.58; $p = 0.003$). The estimated cumulative incidence of peritoneal cancer was 4.3% at 20 years after oophorectomy.

An additional benefit of prophylactic oophorectomy is a marked reduction in the risk of breast cancer. Oophorectomy performed at a relatively early age (<40) is associated with a greater degree of protection than surgery performed near the age of menopause, and the protective effect is evident for 15 years post-oophorectomy. In the largest study to date, Eiesen et al. found that oophorectomy was associated with a significant reduction in breast cancer risk of 56% for BRCA1 carriers and of 46% for BRCA2 carriers. Reductions of similar magnitude have been reported in other studies.

Hormone Replacement Therapy

Premenopausal oophorectomy is associated with the induction of acute menopause. There is concern that the use of hormone replacement therapy in these women may be associated with an increased risk of breast cancer, or may offset the protective effect of the oophorectomy itself. Rebbeck et al. estimated the effect of oophorectomy on breast cancer risk in a study of 462 BRCA1 and BRCA2 carriers. They found that the odds ratio for breast

cancer associated with oophorectomy in the entire study group was 0.40 (95% CI: 0.18 to 0.92) and was 0.37 (95% CI: 0.14 to 0.96) in the subgroup of women with oophorectomy who used hormone replacement therapy.

Oral Contraceptives and Tubal Ligation

A protective effect of oral contraceptives against ovarian cancer has been reported in BRCA carriers. In a recent matched case-control study of 799 ovarian cancer cases and 2,424 controls, 3 to 5 years of oral contraceptive use was associated with a 64% reduction in the risk of ovarian cancer ($p = 0.0001$). In a second, smaller study, 6 or more years of use of oral contraceptives was associated with a decreased in risk of 38% (OR = 0.62; 95% CI: 0.35 to 1.09). Tubal ligation has been found to be protective against ovarian cancer in the general population. There is some evidence that it is also effective among BRCA1 carriers.

Screening for Hereditary Ovarian Cancer

Screening for ovarian cancer using serial CA-125 levels and abdominal ultrasound has been proposed as a method of reducing mortality through early detection. There have been no randomized trials of screening in BRCA1 carriers, but observational cohort studies have been disappointing. Neither CA-125 nor ultrasound have proven to be sensitive means of detecting stage I and stage II ovarian cancers.

ENDOMETRIAL CANCER

KEY POINTS

- Hereditary familial nonpolyposis colon cancer (HNPCC) increases the risks of both endometrial and colon cancer in women.
- Prophylactic hysterectomy is an effective method of endometrial and ovarian cancer risk reduction for mutation carriers.
- Endometrial cancer screening remains unproven in patients with HNPCC.

Genetic Epidemiology

The most important factor in the etiology of endometrial cancer is prolonged estrogen exposure, but inherited factors are important for a small proportion of cases. Susceptibility genes for endometrial cancer include BRCA1, PTEN, and the three mismatch repair genes MSH2, MLH1, and MSH6. These genes are responsible for the hereditary breast-ovarian cancer syndrome, Cowden syndrome, and hereditary nonpolyposis colon cancer, respectively (discussed below).

The Breast Cancer Linkage Consortium reported that some endometrial cancers were due to mutations in BRCA1 but none were due to mutations in BRCA2. However, two smaller studies (one of patients with papillary serous endometrial tumors and one on patients with endometrial carcinomas in general) concluded that the risk of endometrial carcinoma in women with a germ-line BRCA1 mutation was not increased. These findings suggest that it is likely that some cases of endometrial carcinoma are due to an inherited BRCA1 mutation, but the penetrance of BRCA1 mutations for endometrial carcinoma is low and the hereditary fraction is small. Data suggest that the excess risk of endometrial cancer among BRCA carriers can be attributed to past tamoxifen use, and not to the effect of the gene.

Somatic mutations in PTEN are common in endometrial cancers and rarely inherited constitutional mutations in PTEN are present in women with endometrial cancer. In the latter case, endometrial cancer is seen in the context of Cowden syndrome—a rare dominant disease of the skin that is associated with increased risks of cancer of the breast, thyroid gland, and the endometrium.

Women in families with the syndrome of hereditary familial nonpolyposis colon cancer (HNPCC) are also at elevated risk for endometrial and ovarian cancer. This syndrome is characterized by an autosomal dominant inherited tendency to develop colon and other cancers. The colon cancers tend to be of young onset, right sided and are often multicentric. Individuals in families with HNPCC are at risk for a range of cancer types, and endometrial cancer is the second most frequent site of cancer among women. Genes that are responsible for the repair of mismatched DNA (mismatch repair) are defective in families with this syndrome. MSH2, MLH1, and MSH6 are the three major genes responsible for it. The risk of colon cancer is high in families with a mutation in any of these genes, and the lifetime risk for endometrial in women from these families is reported to be from 40% to 60%. The risk of endometrial cancer also depends on which gene carries the mutation. Mutations in MSH2 and MSH6 have been implicated in most HNPCC families with endometrial cancer, but families with MLH1 mutations have been reported as well. Germ-line mutations in MSH6 are relatively rare in HNPCC but are overrepresented in families with multiple cases of endometrial cancer. Goodfellow et al. reported that an inactivating germ-line MSH6 mutation was present in 7 of 441 women with unselected endometrial cancer (1.6%). Cancers were diagnosed in women with mutations on average 10 years earlier than in women without mutations.

Clinical Care and Treatment

The majority of tumors from individuals from HNPCC families demonstrate microsatellite instability. Microsatellite instability is a feature of tumors that are genetically unstable, that is, that are associated with an error-prone DNA replication during cell division. Approximately one-quarter of women with nonhereditary endometrial cancer (sporadic cancer) have tumors that demonstrate microsatellite instability. If the mutation is present in the germ line, it may be transmitted from the carrier parent

to child. In this case, genetic counseling is warranted. It is not necessary that genetic counseling be undertaken when the mutation is limited to the tumor tissue only, as this situation does not pose a risk to relatives. Individuals with an inherited mutation in one of the mismatch repair genes are also at risk for additional cancers, including ovarian, gastric, urologic tract, and small bowel cancers, but the risk for these is much less than for the risk of colon or endometrial cancer. Members of the International Collaborative Group on HNPCC collected information on 80 women with ovarian cancer who were members of HNPCC families. The mean age of diagnosis was 43 years. The majority of cancers were moderately or well differentiated and 85% were stage I or II. Synchronous endometrial cancer was reported in 22% of cases.

There is currently no consensus on the screening and management of women with inherited mutations in the mismatch repair genes. Annual endometrial ultrasound surveillance has been recommended by the International Collaborative Group on HNPCC, but the effectiveness of this screening regimen has not been established. Because of the high lifetime risk of endometrial cancer in women with mutations in the mismatch repair genes, preventive hysterectomy may be warranted.

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CHAPTER 4 ■ PREINVASIVE LESIONS OF THE GENITAL TRACT

PATHOGENESIS AND DIAGNOSIS OF PREINVASIVE LESIONS OF THE LOWER GENITAL TRACT

The high level of public and professional interest in various aspects of preinvasive lesions of the lower genital tract is due to many factors. Perhaps the most important is the marked increase over the last four decades in the number of patients in North America and Western Europe diagnosed with human papillomavirus (HPV)–associated disease. This increase is due partly to a heightened awareness of various clinical and pathologic manifestations of HPV infections, the recent introduction of prophylactic vaccines against specific high-risk types of HPV, and to the increased use of highly sensitive tests for the detection of HPV infections and cervical cancer precursors. In addition, a real increase in the prevalence of HPV infections appears to have taken place during this time. Over half of men and women who are sexually active will be infected at some point in their lives.

Cervix—Squamous Lesions

For more than a century, it has been recognized that invasive squamous cell carcinomas of the cervix are associated with lesions that are histologically and cytologically identical to invasive cervical carcinoma but lack the capacity to invade the subepithelial stroma. These intraepithelial lesions were referred to as *carcinoma in situ*. It also became clear that there were squamous epithelial abnormalities whose histologic and cytologic features were less severe than carcinoma *in situ*. These lesions were referred to as *dysplasia* and were often divided into three grades (e.g., *mild*, *moderate*, or *severe*). Dysplastic lesions, carcinoma *in situ*, and invasive carcinoma form a continuum rather than a series of discrete steps. In 1973, based on follow-up studies of patients with cervical cancer precursor lesions and studies of the biology of these lesions, Richart proposed that the term *cervical intraepithelial neoplasia* (CIN) be used to encompass all forms of cervical cancer precursor lesions, including dysplasia and carcinoma *in situ*.

Cervix—Glandular Lesions

Interest in glandular lesions of the cervix has been stimulated by an apparent increase in the number of women, especially those under the age of 35, who are being diagnosed with invasive adenocarcinoma of the cervix

and glandular precursor lesions. However, the absolute number of invasive adenocarcinomas has not actually increased when women of all age groups are combined. Instead, the number of women with invasive squamous cell carcinomas has decreased, producing a relative increase. It is important to note that although there is considerable evidence indicating that adenocarcinoma *in situ* (AIS) is a precursor for invasive adenocarcinoma of the cervix, there is little evidence to support such a role for the lower-grade glandular abnormalities.

Vulva and Vagina

The nomenclature used for preinvasive lesions of the vulva and vagina has tended to parallel that used for the cervix. In the 1980s, many clinicians and pathologists began to apply the intraepithelial neoplasia terminology widely used for describing cervical cancer precursors to the vulva. Thus the term *vulvar intraepithelial neoplasia* (VIN), together with a grade of 1 to 3, was adopted. Similarly, the term *vaginal intraepithelial neoplasia* (VAIN), together with a grade of 1 to 3, is widely used to describe preinvasive lesions of the vagina. It should be pointed out, however, that data that suggest a continuum between all grades of vulvar and vaginal preinvasive lesions and invasive squamous cell carcinoma at these sites are significantly less compelling than that for the cervix.

NATURAL HISTORY OF PREINVASIVE LESIONS OF THE LOWER GENITAL TRACT

KEY POINTS

- Dysplasia is a precursor to invasive squamous cell carcinoma of the cervix.
- The time required for progression from dysplasia to carcinoma is controversial.
- A smaller portion of vulvar carcinomas arise from precursor lesions.

Cervix

A variety of epidemiologic and long-term follow-up studies supports the concept that certain epithelial lesions are precursors of invasive squamous cell carcinoma of the cervix. A number of follow-up studies clearly demonstrate that, once established, carcinoma *in situ* has a significant potential for progression to invasive cancer, and progression is a slow process, usually requiring a decade or more. Whether carcinoma *in situ*, once established, can spontaneously regress in the absence of therapy is controversial.

TABLE 4.1

NATURAL HISTORY OF CIN IS DEPENDENT ON LESIONAL GRADE

	% Regression	% Persist	% Progress to CIS
CIN 1	57	32	11
CIN 2	43	35	22
CIN 3	32	56	12

Many prospective studies have also followed the transitions between different grades of CIN. These studies have obtained quite different estimates of the frequency of mild dysplasia, the likelihood of progression from low-grade to high-grade precursors, and the time required for this progression. Until recently, it was generally believed that it took many years for a low-grade lesion to progress to a high-grade lesion. Mathematical modeling studies based on the prevalence of cytologic abnormalities in an unscreened population suggested that it takes on average almost 5 years for a mild dysplasia to progress to carcinoma *in situ*. More recent studies indicate, however, that high-grade lesions can develop quite rapidly after an incident HPV infection. A prospective study of college students found that the median length of time from the first detection of a HPV infection to the detection of CIN 2,3 was only 14.1 months. The finding that CIN 2,3 lesions can develop quite rapidly after initial HPV infections has been confirmed in the HPV vaccine trials. A systematic review of the different studies investigating the natural history of untreated biopsy-confirmed CIN, most of which were conducted in the 1970s and 1980s, found that the higher the grade of lesion, the more likely it is to persist and the less likely it is to regress (Table 4.1).

Vulva

Studies on the natural history of VIN lesions are much fewer than for CIN. Partly because of the paucity of studies, the relationships between VIN and invasive squamous cell carcinoma of the vulva appear to be less straightforward than those documented between CIN and invasive squamous cell carcinoma of the cervix. Unlike the cervix, in which the majority of carcinomas are associated with a CIN lesion, only a third of invasive vulvar squamous carcinomas have a coexisting VIN 3 lesion. A review of six published follow-up studies found that only 16 of 330 patients (4.8%) with VIN progressed to invasive cancer. What is generally not emphasized when the data are discussed is that most of the patients in these follow-up studies were treated for their VIN or followed for relatively short periods of time.

RISK FACTORS FOR THE DEVELOPMENT OF LOWER GENITAL TRACT CANCERS AND PREINVASIVE LESIONS OF THE LOWER GENITAL TRACT

KEY POINTS

- Smoking and number of sexual partners are the greatest risk factors for cervical cancer and its precursors.
- Human papillomavirus (HPV) infection is acquired through sexual contact and is necessary for the development of cervical cancer and its precursors.
- The majority of HPV-infected women spontaneously clear their infections within 1 to 2 years.

Cervix

Risk Factors

A large number of epidemiologic studies have analyzed risk factors for the development of cervical cancer and its precursors. Although the risk factors are similar for both cervical cancer and its precursors, the association with the risk factors is generally much stronger for cervical cancer than for precursor lesions. The major risk factors found in most studies are markers of sexual behavior such as number of sexual partners, early age of first pregnancy and first intercourse, sexually transmitted diseases, and parity. In addition, lower socioeconomic class, cigarette smoking, oral contraceptive use, specific HLA-DR haplotypes, and immunosuppression from any cause are associated with both cervical cancer and its precursors.

Human Papillomavirus

Over the last 15 years, considerable evidence has been accumulating rapidly to implicate HPV in the pathogenesis of cervical cancer and its preinvasive precursors. Epidemiologic and molecular studies have found that there is a consistent and strong relationship between HPV infection and cervical neoplasia, that the temporal sequence between the infection and the development of cancer is correct, that the association between HPV and cervical cancer is relatively specific, and that the epidemiologic findings are consistent with the natural history and biologic behavior of HPV infections and cervical cancer.

Epidemiologic studies clearly demonstrate that there is a strong and consistent association between specific types of HPV DNA and invasive cervical cancer and its precursor lesions, and that exposure to HPV precedes the development of cervical disease. When combined with the enormous body of molecular evidence demonstrating a role for HPV in the

development of cervical cancer and CIN, these findings clearly indicate that HPV infection, acquired through sexual contact, is a “necessary cause” of both CIN and invasive cervical cancer. Based on this data, the International Agency for Research on Cancer of the World Health Organization has classified HPV 16 and 18 and all of the other “high-risk” types of HPV as carcinogens in humans.

Smoking and Oral Contraceptives

In addition to risk factors associated with sexual behavior, several other risk factors such as low socioeconomic class and cigarette smoking have also been associated with the development of cervical cancer. The use of combined oral contraceptives has also been found to be a risk factor for the development of cervical cancer and its precursors in some studies. A recent reanalysis of epidemiologic studies involving over 50,000 women confirmed an increase risk of cervical cancer in oral contraceptive users.

Immunosuppression

Immunosuppression is another risk factor for the development of both CIN and cervical cancer. In studies of patients with renal transplants, transplant recipients have a relative risk of 13.6 for the development of cervical carcinoma *in situ* compared to women in the general population. Over the last decade, it has become widely accepted that there is also an association between cervical disease and infection with the human immunodeficiency virus (HIV). Among women in New York City, the standardized incidence ratio for cervical cancer is 9.2 times higher in HIV-infected women compared to noninfected women. It is clear that the invasive cervical cancers that do develop in HIV-infected women act aggressively and respond poorly to standard forms of therapy. Invasive cervical cancer was designated in 1993 as an AIDS case-defining illness by the Centers for Disease Control and Prevention.

HUMAN PAPILLOMAVIRUS

Classification

Papillomaviruses are a diverse group of viruses that are widely distributed in mammals and birds. Papillomavirus isolates are traditionally described as *types*. The characteristic features of papillomaviruses are a double-stranded, circular DNA genome of about 8,000 base pairs, a nonenveloped virion, and an icosahedral capsid. To date, 118 papillomavirus types have been completely described. Over 30 types of HPV that infect the anogenital tract have been described. These different types of HPV tend to be associated with different types of lesions. HPV 6 and 11 are the most common HPV types found in association with exophytic condylomas of the male and female anogenital tracts in adults.

TABLE 4.2

CLASSIFICATION OF ANOGENITAL HPV TYPES

“Low-risk” types	6, 11, 40, 42, 43, 44, 53 ^a , 54, 61, 72, and 81
“High-risk” types	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 82
Possible high-risk types	26, 66, and 73

^aClassified as “low-risk” based on other data.

Source: From Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348:518.

Almost half of all CIN 2,3 lesions are associated with HPV 16. A meta-analysis of the distribution of HPV types in CIN 2,3 lesions recently concluded that HPV 16 is identified in 45.3%, HPV 18 in 6.9%, and HPV 31 in 8.6%. Based on their associations with benign epithelial proliferations, high-grade cancer precursors, or invasive cancers of the vulva, vagina, anus, and cervix, HPVs can be categorized into “high-risk” or “low-risk” based on the relative risk of being associated with cancer (Table 4.2).

PREVALENCE AND TRANSMISSION OF HPV INFECTIONS

The prevalence of genital tract HPV infections and the frequency of exposure to HPV in the general population vary widely in different studies. In nonpregnant women with normal Pap smears, studies have detected HPV DNA in cervical samples in 4% to 43% of women. When multiple samples are taken over time, the cumulative prevalence in cytologically negative women is generally considerably higher. It is clear that the prevalence of HPV infection in the general population is consistently higher than the prevalence of CIN, by about one order of magnitude. The majority of women who are infected with HPV will never develop CIN 2,3 or cancer.

Both genital and non-genital HPV appear to be transmitted predominantly through close “skin-to-skin” or “mucosa-to-mucosa” contact and transmission is facilitated by minor trauma at the site of inoculation. The importance of sexual transmission is highlighted by studies of young women initiating sexual activity. In a study of 604 women attending a university, HPV DNA was detected by PCR in only 3% of women reporting no prior vaginal intercourse, 7% of women with 1 male sexual partner, 33% of women with 2 to 4 partners, and 53% of women with 5 or more male partners.

OUTCOME AFTER EXPOSURE TO HPV

Infection with a high-risk anogenital HPV in most women leads to a transient productive viral infection that lasts for a period of months to years. Approximately one third of these women develop low-grade cytologic or histologic changes. Nevertheless, the vast majority of HPV-infected women spontaneously clear their infections within 1 to 2 years. Clearance appears to be mediated by cellular immune responses. Prospective follow-up studies report that less than 20% of women remain DNA positive after 24 months of follow-up (Table 4.3).

It is currently unknown what proportion of women who appear to spontaneously clear their HPV infections and become HPV DNA negative truly clear the infection from the anogenital tract and what proportion continue to have a latent, undetectable HPV infection.

Reactivation of latent infections could explain the increase in the prevalence of HPV among cytologically negative older women (Fig. 4.1).

Although spontaneous clearance can continue to occur even after 24 months, clinically significant persistent infections should probably be defined as infections that last at least 2 years. Long-term, stable persistent infections appear to occur in only about 10% of infected individuals. Although newer studies suggest that CIN 2,3 lesions can develop within a relatively short period of time after initial infection, lesions that do not persist for at least 2 years are unlikely to have clinical significance.

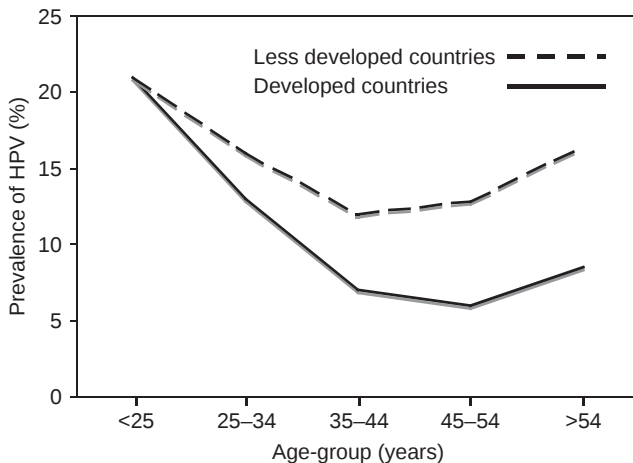


FIGURE 4.1. Estimate of prevalence of HPV DNA positivity in women with normal cervical cytology. The estimate is based on a meta-analysis that included published studies from all regions of the world.

Source: Adapted from de Sanjose S, Diaz M, Casellsague X, et al. Worldwide prevalence and genotype distribution of cervical HPV DNA in women with normal cytology: A metaanalysis. *Lancet Infect Dis.* 2007;7(7):453-459.

TABLE 4.3
PREVALENCE AND CUMULATIVE DETECTION RATES OF HPV IN YOUNG WOMEN

Author	No. of Patients	Mean Age (years)	Type of Infection	% Persistent at		
				6 months	12 months	24 months
Sun et al.	231	34	Incident and prevalent	50%	35%	18%
Ho et al.	608	20	Incident	—	30%	8%
Moscicki et al.	618	20	Prevalent	50%	30%	10%
Woodman et al.	1,075	20	Incident	24%	4%	<1%
Richardson et al.	635	23	Incident	—	62%	—

Sources: Adapted from Sun XW, Kuhn L, Ellerbrock TV, et al. Human papillomavirus infection in women infected with the human immunodeficiency virus. *N Engl J Med.* 1997;337:1343; Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338:423; Moscicki AB, Hills N, Shiboski S, et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *JAMA.* 2001;285:2995; Woodman CB, Collins S, Winter H, et al. Natural history of cervical human papillomavirus infection in young women: A longitudinal cohort study. *Lancet.* 2001;357:1831; Richardson H, Kelsall G, Tellier P, et al. The natural history of type-specific human papillomavirus infections in female university students. *Cancer Epidemiol Biomarkers Prev.* 2003;12:485.

CYTOLOGIC SCREENING FOR CERVICAL CANCER AND ITS PRECURSORS

KEY POINTS

- Cervical cytology has reduced the incidence of cervical cancer by almost 80% in the United States.
- Cervical screening should begin 3 years after the initiation of sexual intercourse, but no later than age 21 years.
- Liquid-based pap smears have the advantage of providing reflex human papillomavirus testing in women with atypical squamous cells of undetermined significance.

Cytology-based cervical cancer screening programs were first introduced in the mid-20th century and are now widely recognized as being able to reduce both the incidence of, and mortality from, invasive cervical cancer. Strong evidence for their effectiveness comes from a comparison of incidence and mortality trends of invasive cervical cancer with screening activity in a given country or region.

Accuracy of Cervical Cytology

Despite the proven effectiveness of cervical cytology in reducing the incidence of cervical cancer, over the last several years the accuracy of cervical cytology has been questioned. However, when the cytologic cutoff is low-grade squamous intraepithelial lesion (LSIL) and the endpoint is biopsy-confirmed CIN 2,3 or worse, the average sensitivity is 81% and the specificity is 77%.

A number of factors influence the false-negative rate of cervical cytology. Since the majority of CIN and cancers involve the transformation zone, sampling devices have been specifically designed to sample this area. Sampling the endocervical canal reduces the false-negative rate. This sample can be taken with an endocervical brush (e.g., cytobrush) or one of the newer collection devices such as a cell broom. Saline-moistened cotton-tipped applicators should not be used. Other important factors for reducing the false-negative rate are the rapid fixation of cells to prevent artifactual changes secondary to air-drying and the use of a cytology laboratory with stringent quality control standards.

The use of cervical cytology has reduced the incidence of cervical cancer by almost 80% in the United States over the last three decades. The effectiveness of cervical cytology is attributable to the fact that invasive cervical cancer requires many years to develop from a CIN 2,3 lesion. If cervical cytology is performed on an routine basis, it is unlikely that a CIN 2,3 lesion will remain undetected, although such cases do rarely occur. The current screening recommendation from the American Cancer Society and the American College of Obstetricians and Gynecologists is that cervical cancer screening should be initiated approximately 3 years after

the initiation of sexual intercourse, but no later than age 21 years. After 30 years of age, the interval between cervical cytology examinations can be extended to 2 to 3 years in women who have had three consecutive negative cervical cytology screening test results, who have no history of CIN 2,3 and are neither immunocompromised nor exposed to diethylstilbestrol (DES). There is currently no consensus as to when to stop screening. Routine screening is not recommended for women who have undergone a hysterectomy for benign indications and who have no prior history of CIN 2,3.

Liquid-based Cytology

Liquid-based cytology (LBC) is now widely used in the United States for cervical cytology. A major reappraisal of the performance of LBC is under way in the screening community. When it was first introduced, LBC was believed to provide a significant advantage compared to conventional cervical cytology with respect to sensitivity for the identification of women with CIN 2,3 or cancer. However, most of the studies that compared LBC with conventional cytology had methodological problems. When all of the studies are taken into account and combined, it was concluded that they saw no evidence that LBC reduced the proportion of unsatisfactory slides nor that it has better performance than conventional cytology with respect to the identification of women with CIN 2,3.

There is no evidence that LBC is either more sensitive or more specific than conventional cytology. Having said this, it is important for clinicians to recognize that there are other advantages of LBC. The greatest of these appears to be the availability of residual fluid for “reflex” HPV testing in women with atypical squamous cells of undetermined significance (ASC-US) as well as testing for other pathogens such as Chlamydia. Moreover, almost all cytologists agree that it is easier to evaluate LBC specimens than conventional cytology specimens and it is unlikely that cytology laboratories will want to switch back to conventional cytology now that the conversion to LBC has taken place.

Terminology of Cytologic Reports

The Bethesda System terminology is used for reporting cervical cytology results in the United States. The Bethesda System underwent significant modifications in 2001 (Table 4.4). The major features of the 2001 Bethesda System are that it requires (i) an estimate of the adequacy of the specimen for diagnostic evaluation; (ii) a general categorization of the specimen as being either “negative for intraepithelial lesion or malignancy,” as having an “epithelial cell abnormality,” or as “other” (i.e., having endometrial cells in a woman 40 years of age and older); and (iii) a descriptive diagnosis that includes a description of epithelial cell abnormalities. The terms LSIL and *high-grade squamous intraepithelial lesion* (HSIL) are used to designate cytologic changes that correlate with CIN 1 and CIN 2,3, respectively. In addition, the Bethesda System attempts to separate epithelial changes secondary to inflammation or repair from those associated with cervical

TABLE 4.4

THE 2001 BETHESDA SYSTEM

SPECIMEN ADEQUACY

Satisfactory for evaluation (*note presence/absence of endocervical transformation zone component*)

Unsatisfactory for evaluation (*specify reason*)

Specimen rejected/not processed (*specify reason*)

Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

GENERAL CATEGORIZATION (OPTIONAL)

Negative for intraepithelial lesion or malignancy

Epithelial cell abnormality

Other

INTERPRETATION/RESULT

Negative for intraepithelial lesion or malignancy

Organisms

Trichomonas vaginalis

Fungal organisms morphologically consistent with *Candida* species

Shift in flora suggestive of bacterial vaginosis

Bacteria morphologically consistent with *Actinomyces* species

Cellular changes consistent with herpes simplex virus

Other nonneoplastic findings (*optional to report; list not comprehensive*)

Reactive cellular changes associated with inflammation (includes typical repair)

Radiation

Intrauterine contraceptive device

Glandular cells status posthysterectomy

Atrophy

Epithelial cell abnormalities

Squamous cell

ASC-US; cannot exclude HSIL (ASC-H)

LSIL

HSIL

Squamous cell carcinoma

Glandular cell

AGC (*specify endocervical, endometrial, or not otherwise specified*)

AGCs, favor neoplastic (*specify endocervical or not otherwise specified*)

Endocervical AIS

Adenocarcinoma

Other (*list not comprehensive*)

Endometrial cells in a woman ≥ 40 years of age

Source: Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology. *JAMA*. 2002;287:2114.

cancer precursors whenever possible. Nondiagnostic squamous cell abnormalities are included in a category of *atypical squamous cells* (ASC). ASC is used when a specimen has features suggestive, but not diagnostic, of a SIL. This category is further subdivided into two subcategories: ASC-US and ASC—cannot exclude HSIL (ASC-H). The risk of a woman with ASC-US having biopsy-confirmed CIN 2,3 is approximately 7% to 17%, and the risk for a woman with ASC-H is approximately 40%. Nondiagnostic glandular cell abnormalities are included in a category of *atypical glandular cells* (AGC). This category is further subdivided into either *not further classified* or AGC—*favor neoplasia*.

USE OF COLPOSCOPY

Over the last 25 years, colposcopy combined with colposcopically directed cervical biopsies have become the primary modality by which women with abnormal Pap smears are evaluated. Colposcopic examination consists of viewing the cervix with a long-focal-length, dissecting-type microscope after a solution of dilute (4%) acetic acid has been applied to the cervix. The acetic acid solution acts to remove and dissolve the cervical mucus and causes CIN lesions to become whiter than the surrounding epithelium (acetowhite). This coloration allows the colposcopist to identify and biopsy epithelial lesions. In addition to allowing the detection of acetowhite areas, colposcopy also allows for the detection of blood vessel patterns that can indicate high-grade CIN lesions and the detection of invasive cancers. Colposcopy and appropriately directed biopsy have greatly facilitated the management of patients with preinvasive lesions of the cervix because it allows the clinician to rule out invasive cancer and determine the limits of preinvasive disease.

MANAGEMENT OF CYTOLOGIC ABNORMALITIES AND CIN

KEY POINTS

- Complete recommendations and management algorithms are available at www.asccp.org.
- Over 90% of low-grade squamous intraepithelial lesion will spontaneously clear in adolescents.
- A diagnosis of high-grade squamous intraepithelial lesion confers a significant risk for CIN 2,3 and invasive cervical cancer.

In 2006, the American Society for Colposcopy and Cervical Pathology sponsored a consensus workshop to update the 2001 Consensus Guidelines for the Management of Women with Cytological Abnormalities and Cervical Cancer Precursors. These guidelines are widely used in the United

States and are evidence based, with each recommendation accompanied by a grading of both the strength of the recommendation and the strength of the data supporting the recommendation. The complete recommendations and management algorithms are available at www.asccp.org.

Atypical Squamous Cells

A vexing group of patients for both clinicians and cytologists are those whose cervical cytology is atypical (i.e., not normal) but lack the characteristic features of SIL or cancer. Clinicians need to be aware that a cytologic result of ASC is the least reproducible cytologic category. In the most recent report from the College of American Pathologists, the median ASC rate from reporting laboratories from the United States was 5%.

The prevalence of biopsy-confirmed CIN 2,3 found in women undergoing colposcopy for an ASC cytology is generally reported as being 5% to 17%. In the large, multicenter ASC-US/LSIL Triage Study (ALTS), 15% of the women referred with ASC were found to have biopsy-confirmed CIN 2,3 at the initial colposcopic examination, and 20% had biopsy-confirmed CIN 1. Overall, it appears that between one-third and one-half of all women diagnosed as having CIN 2,3 have ASC as their initial abnormal cervical cytology result. Although the risk that a woman with ASC has invasive cervical cancer is quite low (about 1/1,000), the very large number of women with this cytology interpretation (2.5 million annually) guarantees that each year approximately 2,500 women with invasive cervical cancer will have only equivocal results on their cervical cytology. Therefore, women with ASC-US need to receive some form of follow-up evaluation, but consideration should be given to preventing unnecessary inconvenience, anxiety, cost and discomfort.

Atypical Squamous Cells of Undetermined Significance

Three methods are in widespread use for the management of women with ASC. These are immediate colposcopy, HPV DNA testing, and a program of repeat cervical cytology. A number of studies have directly compared the sensitivity and specificity of repeat cervical cytology and HPV DNA testing for identifying women with CIN 2,3. In every single study, HPV DNA testing identified more cases of CIN 2,3 than did a single repeat cervical cytology, but referred approximately equivalent numbers of women for colposcopy. The 2002 ASCCP Consensus Conference concluded that although all three of the methods traditionally used to manage women with ASC-US (i.e., colposcopy, repeat cytology, and HPV DNA testing) are safe and effective, high-risk HPV DNA testing is the preferred approach to managing women with ASC-US whenever LBC is used for screening or co-collection of a sample for HPV DNA testing can be performed. Figure 4.2 provides the algorithm recommended for the management of women in the general population with ASC-US. This algorithm is appropriate for women of all ages with ASC-US.

The prevalence of HPV DNA positivity is much higher in young women with ASC-US than in older women. Therefore, the 2006 Consensus Guidelines do not recommend the use of HPV DNA testing in adolescents,

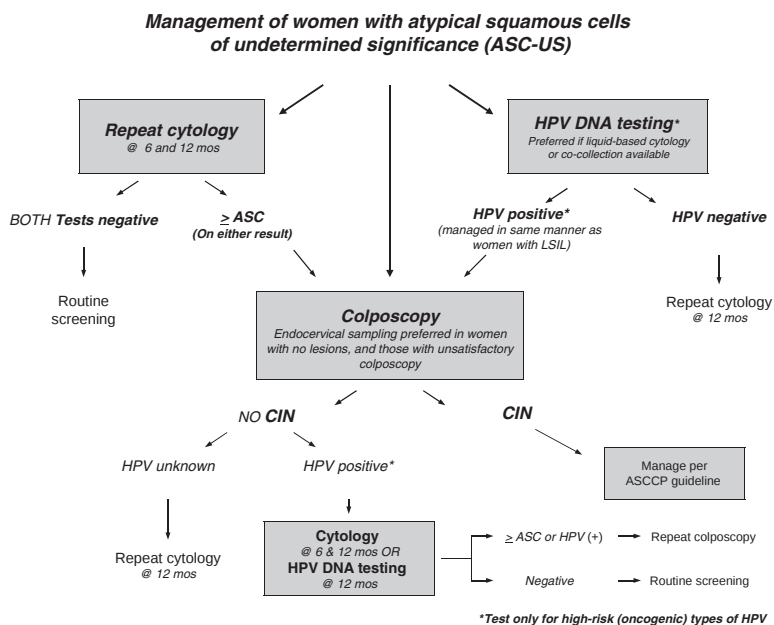


FIGURE 4.2. 2006 Consensus Guidelines for the management of women with ASC-US. Used with permission from the American Society of Colposcopy and Cervical Pathology.

defined as females 13 to 20 years of age. Instead, adolescents should be managed using annual repeat cytologic examinations and only referred to colposcopy if the repeat Pap tests are diagnosed as HSIL or are persistently abnormal for a period of 2 years.

Management options for pregnant patients with ASC-US are identical to those for nonpregnant patients with the exception that it is acceptable to defer the colposcopic examination until the patient is 6 to 8 weeks postpartum.

Atypical Squamous Cells—Cannot Exclude HSIL

The prevalence of biopsy-confirmed CIN 2,3 is considerably higher among women referred for the evaluation of an ASC-H cervical cytology than it is for women referred for the evaluation of ASC-US. CIN 2,3 is identified in 24% to 94% of women with ASC-H. Therefore, for the purposes of management, ASC-H should be considered to be an equivocal HSIL result. Because of this high risk, the 2006 Consensus Guidelines recommend that all women with ASC-H be referred for a colposcopic evaluation. If CIN is not identified, follow-up utilizing either repeat cytology at 6 and 12 months or high-risk HPV DNA testing at 12 months is acceptable (Fig. 4.3).

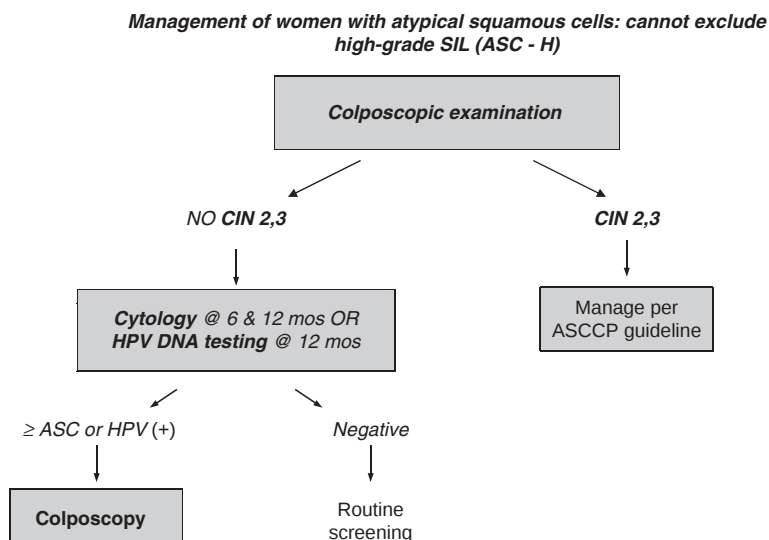


FIGURE 4.3. 2006 Consensus Guidelines for the management of women with ASC-H. Used with permission from the American Society of Colposcopy and Cervical Pathology.

Low-grade Squamous Intraepithelial Lesions

As with ASC-US, there is considerable variation between populations and laboratories in the rate at which LSIL is reported. A cytologic result of LSIL is a very specific indicator of the presence of high-risk types of HPV. In ALTS, 83% of the women referred for the evaluation of LSIL were high-risk HPV DNA positive. However, a cytologic result of LSIL is a poor predictor of the grade of CIN that will be identified at colposcopy. CIN 2,3 is identified at colposcopy in 15% to 30% of women with LSIL on cervical cytology. Therefore, the 2006 Consensus Guidelines recommend that all women in the general population with a cytologic result of LSIL be referred for a colposcopic evaluation (Fig. 4.4). This allows women with significant disease to be rapidly identified and reduces the risk of women being lost to follow-up. A diagnostic excisional procedure is not required when a woman with LSIL cytology is found to have an unsatisfactory colposcopic examination.

The risk of invasive cervical cancer is very low in adolescents, and prospective studies have shown that over 90% of LSIL will spontaneously clear in over a period of years in adolescents. Therefore, adolescents with LSIL (<21 years of age) are considered to be a “special population,” and it is now recommended that they should not receive colposcopy, but instead should be followed using yearly Pap tests for a period of 2 years. Another “special population” is postmenopausal women with LSIL. In some studies, the prevalence of HPV DNA in postmenopausal women with LSIL is lower than

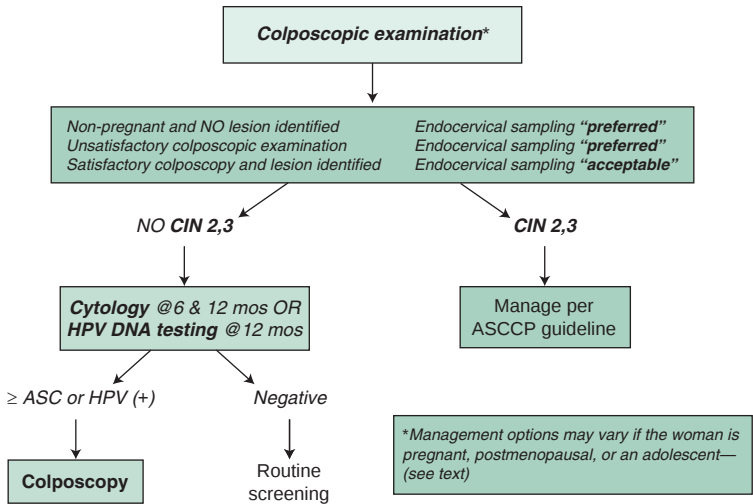


FIGURE 4.4. 2006 Consensus Guidelines for the management of women with LSIL. Used with permission from the American Society of Colposcopy and Cervical Pathology.

in premenopausal women, and the prevalence of CIN 2,3 also declines in postmenopausal women with LSIL. Therefore, the 2006 Consensus Guidelines indicate that postmenopausal women with LSIL can be managed in the same manner as women with ASC-US. This allows the use of reflex HPV DNA testing to determine which of these women require colposcopy.

High-grade Squamous Intraepithelial Lesions

The cytologic result of HSIL is uncommon, accounting for only about 0.7% of all cervical cytology results, but the prevalence varies with age. A diagnosis of HSIL confers a significant risk for CIN 2,3 and invasive cervical cancer. CIN 2,3 or cancer has been identified at a single colposcopic examination in 53% to 66% of women with HSIL and in 84% to 97% of those evaluated using a loop electrosurgical excisional procedure (LEEP). Invasive cervical cancer is identified in approximately 2% of women with HSIL. Therefore, women with a cytologic result of HSIL should be referred for either a colposcopic evaluation or an immediate LEEP (Fig. 4.5). Subsequent management depends on whether or not the patient is pregnant and whether the colposcopic examination is satisfactory.

Biopsy-confirmed CIN 1

Women with a histologically confirmed CIN 1 lesion represent a heterogeneous group. A number of studies have clearly demonstrated a high level of variability in the histologic diagnosis of CIN 1. In ALTS, only 43% of biopsies that

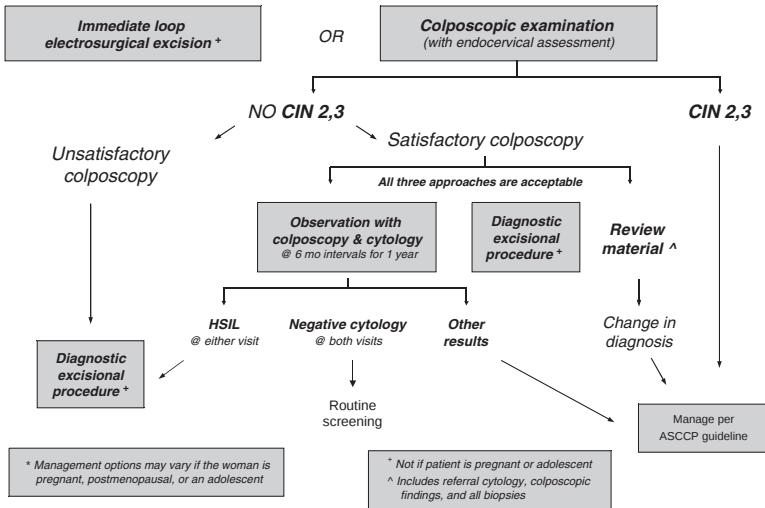
Management of women with high-grade squamous intraepithelial lesions (HSIL) *

FIGURE 4.5. 2006 Consensus Guidelines for the management of women with HSIL. Used with permission from the American Society of Colposcopy and Cervical Pathology.

were originally diagnosed as CIN 1 at the clinical centers were subsequently classified as CIN 1 by the reference pathology committee. Forty-one percent were downgraded to normal and 13% were upgraded to CIN 2,3. It should also be noted that there is a very high rate of spontaneous regress of CIN 1 in the absence of treatment. One prospective Brazilian study found that 90% of women with a cytologic diagnosis of LSIL spontaneously regressed within 24 months. Recent studies indicate that CIN 1 only rarely progresses to CIN 2,3. Since the risk of an undetected CIN 2,3 or glandular lesion is expected to be higher in women referred for the evaluation of a HSIL or AGC on cytology, women with CIN 1 preceded by HSIL or AGC cervical cytology can be managed more aggressively than women with CIN 1 preceded by ASC-US, ASC-H, or LSIL cytology. If CIN 1 persists for at least 2 years, either continued follow-up or treatment is acceptable. Randomized controlled clinical trials comparing cryotherapy, laser ablation, and LEEP for treating biopsy-confirmed CIN have reported no significant differences in either complication rates or success rates. Before treating any grade of CIN using an ablative modality such as cryotherapy, it is important to perform an endocervical sampling in order to assure that an unsuspected lesion is not present in the endocervical canal.

Biopsy-confirmed CIN 2,3

Women with an untreated histologically confirmed CIN 2,3 lesion are felt to have a significantly high risk of progressing to invasive cervical cancer to warrant routine treatment. In patients with recurrent CIN (either CIN 1

or CIN 2,3), it is preferred that an excisional treatment modality be used. A diagnostic excisional procedure is recommended for all women with biopsy-confirmed CIN 2,3 and an unsatisfactory colposcopic examination.

The risk of recurrent CIN 2,3 or invasive cancer after treatment remains elevated for many years after treatment. The 2006 Consensus Guidelines recommend that after treatment for CIN 2,3 women be followed up using either (i) HPV DNA testing at 6 to 12 months, (ii) cytology alone at 6 month intervals, or (iii) a combination of cytology and colposcopy at 6 month intervals. After two negative cytology results are obtained, routine screening is recommended for at least 20 years. When CIN is identified at the margins of a diagnostic excisional procedure, it is preferred that the 4- to 6-month follow-up visit include endocervical sampling.

Atypical Glandular Cells

Patients with AGC are at risk for both cervical and endometrial abnormalities. For women under age 35, colposcopy with endocervical curettage should be performed. For women older than 35 or any women with abnormal vaginal bleeding in the setting of AGC, an endometrial biopsy should also be performed. Recent ASCCP guidelines also indicate that HPV testing for high-risk subtypes should be performed. There is a higher risk of dysplastic lesions with AGC than with ASC-US. CIN 1 that develops in the setting of AGC can undergo observation with repeat colposcopy and cytology or a diagnostic excisional procedure. CIN 2,3 should be managed with an excisional procedure, as would be performed for any high-grade biopsy-proven cervical lesion.

Adenocarcinoma *In Situ*

Patients with AIS are known to have both multifocal disease and a risk of invasive adenocarcinoma when thoroughly sampled. Therefore, excision is required for all patients, and due to the risk of invasive disease and an average failure rate of 8% for conservative treatment, failure is defined as recurrent AIS or invasive disease. Hysterectomy is the preferred treatment of choice, but must be preceded by an excisional biopsy that can reasonably exclude invasion that might require a more radical procedure. For women desiring fertility preservation, a cold knife cone biopsy with negative margins is an acceptable alternative.

Vulvar and Vaginal Intraepithelial Neoplasia

VIN and VAIN require more individualization and creativity in treatment. Most VIN is detected at the time of biopsy for a suspicious lesion, and therefore definitive treatment should be complete excision, although positive margins for a low-grade lesion could be observed. Higher grade VIN should be completely excised with negative margins; however, laser ablation would be an acceptable alternative. VAIN treatment must be more tailored to the disease location and patient. In general, VAIN should be treated, though low-grade lesions could be followed akin to biopsy-proven

CIN 1. VAIN 2,3 should be treated, and simple excision is the preferred method as it provides a specimen in which to rule out invasive disease. Topical treatment with intravaginal 5-FU has been used; however, it is associated with serious adverse events and is not recommended as an initial choice of therapy. Laser ablation is a reasonable alternative to excision for diffuse lesions or lesions in regions that are challenging to resect.

Suggested Readings

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- Wright TC Jr, Massad LS, Dunton CJ, et al. 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ. *Am J Obstet Gynecol*. 2007b;197:340.

CHAPTER 5 ■ THE VULVA

Malignant tumors of the vulva account for less than 5% of all cancers of the female genital tract, with an estimated 3,460 new cases and 870 deaths occurring in 2008. The majority of women with vulva cancer initially present with symptoms most commonly reported as irritation, pruritus, pain, or a mass lesion that does not resolve. Diagnosis is frequently delayed due to a combination of patient and physician factors, with one report noting 88% of patients had experienced symptoms for more than 6 months prior to diagnosis. While the traditional therapeutic approach to vulva cancer has been radical surgical excision of the primary tumor and inguinal femoral lymph nodes, a more tailored individualized approach to vulva cancer management, often employing multiple modalities in an effort to achieve excellent disease control with better cosmetic results and sexual function, is now the norm.

HISTOLOGY

The majority of malignant vulva tumors are squamous cell carcinomas, with malignant melanoma being the second most common histology. Basal cell carcinoma, adenocarcinomas (derived from the Bartholin gland, eccrine sweat glands, Paget disease, or ectopic breast tissue), and a host of very rare soft tissue sarcomas including leiomyosarcomas, malignant fibrous histiocytomas, liposarcomas, angiosarcomas, rhabdomyosarcomas, epithelioid sarcomas, and Kaposi sarcomas may also arise on the vulva. Finally, the vulva may be secondarily involved with malignant disease originating in the bladder, anorectum, or other genital organs.

ANATOMY

The vulva consists of the external genital organs including the mons pubis, labia minora and majora, clitoris, vaginal vestibule, perineal body, and their supporting subcutaneous tissues. The Bartholin glands, two small mucus-secreting glands, have ducts opening onto the posterolateral portion of the vestibule. The perineal body is a 3- to 4-cm band of skin and subcutaneous tissue located between the posterior extension of the labia majora and the anus, and forms the posterior margin of the vulva.

The vulva has a rich blood supply derived primarily from the internal pudendal artery, and the superficial and deep external pudendal arteries. The innervation of the vulva is derived from L1 (ilioinguinal nerve),

L1–2 (genitofemoral nerve), and S2–4 (pudendal nerves). The vulva lymphatics run anteriorly through the labia majora, turn laterally at the mons pubis, and drain primarily into the superficial inguinal lymph nodes. The vulva lymphatic channels do not cross the midline, unless the site of dye injection is in midline structures (the clitoris or perineal body). Drainage from midline lesions could be bilateral. Several small lymphatics may drain from the clitoris under the pubic symphysis directly into the pelvic nodes. The superficial inguinal lymph nodes are located within the femoral triangle, which is formed by the inguinal ligament superiorly, the border of the sartorius muscle laterally, and the border of the adductor longus muscle medially. Lymphatic drainage proceeds from the superficial to the deep inguinal (or femoral) nodes and then into the pelvic lymph node basin (Fig. 5.1). There are usually three to five deep nodes, the most superior of which is Cloquet node located under the inguinal ligament.

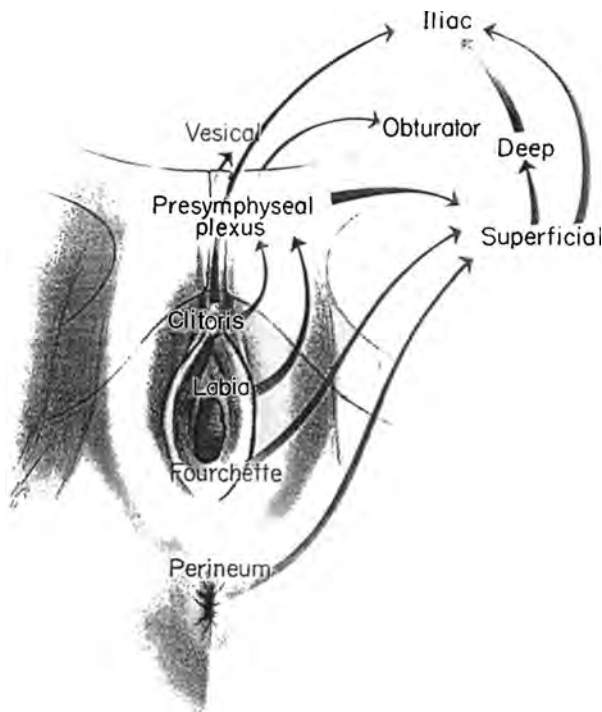


FIGURE 5.1. The lymphatic drainage of the vulva initially flows to the superficial inguinal nodes and then to the deep femoral and iliac groups. Drainage from midline structures may flow directly beneath the symphysis to the pelvic nodes.

Source: Reprinted from Plentl AA, Friedman EA, eds. *Lymphatic System of the Female Genitalia*. Philadelphia, PA: WB Saunders; 1971.

EPIDEMIOLOGY

KEY POINTS

- Vulvar cancer is more common in menopausal women.
- Human papillomavirus is found in 50% or less of invasive tumors.
- All suspicious lesions should be biopsied in the office.
- Vulvar dysplasties may be precursor lesions of invasive disease.

Most vulvar cancers occur in postmenopausal women, although more recent reports suggest a trend toward younger age at diagnosis. Several infectious agents have been proposed as possible etiologic agents in vulvar carcinoma, including granulomatous infections, herpes simplex virus, and human papillomavirus (HPV). HPV DNA has been isolated from both invasive and *carcinoma in situ* lesions, with HPV type 16 being the most common. HPV DNA can be identified in approximately 70% to 80% of intraepithelial lesions, but is seen in only 10% to 50% of invasive lesions.

Several variables have been associated with an increased risk of vulvar cancer including a history of genital condylomata, a previous abnormal Papanicolaou smear, a history of smoking, and chronic immunosuppression. Both chronic vulvar inflammatory lesions, such as vulvar dystrophy or lichen sclerosus, and squamous intraepithelial lesions, particularly *carcinoma in situ*, have been suggested as precursors of invasive squamous cancers.

CLINICAL PRESENTATION

Most women with vulvar cancer present with pruritus and a recognizable lesion. Optimal management for any patient presenting with a suspicious lesion is to proceed directly to biopsy under local analgesia. Tissue biopsies should include the cutaneous lesion in question and contiguous underlying stroma so that the presence and depth of invasion can be accurately assessed. The goals of immediate evaluation with outpatient biopsy are to avoid delay in the planning of appropriate therapy. The presentation in advanced disease is generally dominated by local pain, bleeding, and surface drainage from the tumor.

DIAGNOSTIC EVALUATION

Initial evaluation should include a detailed physical examination with measurements of the primary tumor, assessment for extension to adjacent mucosal or bony structures, and possible involvement of the inguinal lymph nodes. Because neoplasia of the female genital tract is often multifocal, evaluation of the vagina and cervix—include cervical cytologic screening—should always be performed in women with vulvar neoplasms. Fine needle aspiration biopsy from sites of suspected metastases may

eliminate the need for surgical exploration in some patients with advanced tumors.

STAGING SYSTEMS

The International Federation of Gynecology and Obstetrics (FIGO) adopted a modified surgical staging system for vulvar cancer in 1989, which remained relatively unchanged in their 1995 recommendations (Table 5.1). The TNM classification scheme is correlated with the FIGO staging system (Table 5.2).

TABLE 5.1

FIGO STAGING OF CARCINOMA OF THE VULVA (UPDATED 2009)

I	Tumor confined to the vulva
IA	Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm*, no nodal metastasis
IB	Lesions > 2 cm in size or with stromal invasion > 1.0 mm*, confined to the vulva or perineum, with negative nodes
II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes
III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes
IIIA	(i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1–2 lymph node metastasis(es) (< 5 mm)
IIIB	(i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (< 5 mm)
IIIC	With positive nodes with extracapsular spread
IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures
IVA	Tumor invades any of the following: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or (ii) fixed or ulcerated inguino-femoral lymph nodes
IVB	Any distant metastasis including pelvic lymph nodes

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Source: From Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009;105:103-4.

TABLE 5.2**AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGING OF VULVAR CANCER (7TH ED.)****PRIMARY TUMOR (T)**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis*	Carcinoma <i>in situ</i> (preinvasive carcinoma)
T1a	Lesions 2 cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less**
T1b	Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2***	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T3****	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or two regional lymph nodes with the following features
N1a	1 lymph node metastasis 5mm or less
N1b	1 lymph node metastasis 5mm or greater
N2	Regional lymph node metastasis with the following features
N2a	Three or more lymph node metastases each less than 5 mm
N2b	Two or more lymph node metastases 5 mm or greater
N2c	Lymph node metastasis with extracapsular spread
N3	Fixed or ulcerated regional lymph node metastasis
	<i>An effort should be made to describe the site and laterality of lymph node metastases.</i>

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis (including pelvic lymph node metastasis)

ANATOMIC STAGE / PROGNOSTIC GROUPS

Stage 0*	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T1, T2	N1a, N1b	M0
Stage IIIB	T1, T2	N2a, N2b	M0
Stage IIIC	T1, T2	N2c	M0

(continued)

TABLE 5.2

AMERICAN JOINT COMMITTEE ON CANCER (AJCC) STAGING OF VULVAR CANCER (7TH ED.) (*continued*)

ANATOMIC STAGE / PROGNOSTIC GROUPS (<i>cont'd</i>)			
Stage IVA	T1, T2	N3	M0
	T3	Any N	M0
Stage IVB	Any T	Any N	M1

*FIGO no longer includes Stage 0 (Tis).

**The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

***FIGO uses the classification T2/T3. This is defined as T2 in TNM.

****FIGO uses the classification T4. This is defined as T3 in TNM.

Source: Reprinted with permission. AJCC Cancer Staging Manual Edge, S.B.; Byrd, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A. (Eds.), 7th ed., 2010; p. 646.

Nodal status is determined by the surgical evaluation of the groins. The presence or absence of distant metastases is based on an unspecified diagnostic workup tailored to the patient's clinical presentation.

PATTERNS OF SPREAD

Vulvar cancers metastasize in three ways: (i) local growth and extension into adjacent organs; (ii) lymphatic embolization to regional lymph nodes in the groin; and (iii) hematogenous dissemination to distant sites. Descriptive definitions of local extension are clinically useful in that local surgical resection with a wide margin is almost universally feasible in women with T1 or T2 tumors, occasionally possible in those with T3 lesions, and impossible in those with T4 tumors without resorting to an exenterative operation. More recent experience with intraoperative mapping has demonstrated that lymphatic drainage from most vulvar sites proceeds initially to a "sentinel" node located within the superficial inguinal groove.

Inguinal node metastasis can be predicted by the presence of certain parameters, including lesion diameter greater than 2 cm, poor differentiation, increasing depth of stromal invasion, and invasion of lymphovascular spaces. Clinically important observations regarding nodal metastases include the following: (i) the superficial inguinal nodes are the most frequent site of lymphatic metastasis; (ii) in-transit metastases within the vulvar skin are exceedingly rare, suggesting that most initial lymphatic metastases represent embolic phenomena; (iii) metastasis to the contralateral groin or deep pelvic nodes is unusual in the absence of ipsilateral groin metastases; and (iv) nodal involvement generally proceeds in a stepwise fashion from the superficial inguinal to the deep inguinal and then to the pelvic nodes. Spread beyond the inguinal lymph nodes is considered distant metastasis.

PATHOLOGY

KEY POINTS

- Squamous cell carcinoma is the most common histologic subtype.
- Melanoma is the second most common subtype and 25% may be nonpigmented.
- The risk of lymph node metastases is negligible when the depth of invasion is less than or equal to 1 mm.
- Paget disease of the vulva has a high likelihood of recurrence and may be associated with underlying adenocarcinoma.

Most vulvar squamous carcinomas arise within areas of epithelium involved by some recognized epithelial cell abnormality. Approximately 60% of cases have adjacent vulvar intraepithelial neoplasia (VIN). In cases of superficially invasive squamous carcinoma of the vulva, the frequency of adjacent VIN approaches 85%. Lichen sclerosus, usually with associated squamous cell hyperplasia, and/or differentiated VIN, can be found adjacent to vulvar squamous cell carcinoma in 15% to 40% of the cases.

Vulvar squamous cell carcinoma precursors can be considered in two distinct groups: those associated with HPV, usually associated VIN, and those that are not (e.g., those associated with lichen sclerosus, chronic granulomatous disease).

Vulvar Carcinomas

Squamous Cell Carcinomas

The term microinvasive carcinoma is not recognized as meaningful in reference to the vulva because there are no commonly agreed on pathologic criteria established for this term. A substage however, of FIGO stage I, stage IA, is defined as a solitary squamous carcinoma of the vulva measuring 2 cm or less in diameter with clinically negative nodes, with depth of tumor invasion 1 mm or less. Tumors with a depth or thickness of 1 mm or less carry little or no risk of lymph node metastasis. Stage I squamous carcinomas of the vulva, with a reported depth or thickness of 5 mm or more, have a lymph node metastasis rate of 15% or higher. In addition to tumor stage and depth or thickness, other pathologic features include vascular space invasion, growth pattern of the tumor, grade of the tumor, and tumor type.

In a multivariable retrospective analysis of 39 cases of vulvar squamous carcinoma, in addition to clinical stage, and when corrected for treatment modality, pattern of tumor invasion, depth of tumor invasion, and lymph node status were all found to be significant prognostic factors. In addition, desmoplasia (a fibroblastic stromal tumor response) has been correlated with a higher risk of lymph node metastasis and poorer survival.

Verrucous carcinoma of the vulva is an exophytic-appearing growth that can be locally destructive. Clinically, it may resemble condyloma acuminatum. Because of its excellent prognosis, strict histologic criteria

should be used in the diagnosis of verrucous carcinoma. Verrucous tumors may be associated with HPV type 6 or its variants.

Adenocarcinoma and Carcinoma of Bartholin Gland

Most primary adenocarcinomas of the vulva arise within the Bartholin gland. Invasive vulvar Paget disease can give rise to adenocarcinoma. Primary malignant tumors arising within Bartholin gland include adenocarcinoma and squamous cell carcinoma, which occur with approximately equal frequency. Carcinoma of Bartholin gland generally occurs in older women and is rare in women younger than 50. In clinical practice, it is generally advisable to excise an enlarged Bartholin gland in a woman 50 years of age or older, especially if there is no known history of prior Bartholin cyst. If a cyst is drained and a palpable mass persists, excision is also indicated.

Primary carcinomas within the Bartholin gland are characteristically deep in location and difficult to detect in their early growth. Approximately 20% of women with primary carcinoma of Bartholin gland have metastatic tumor to the inguino femoral lymph nodes at the time of primary tumor diagnosis.

Vulvar Paget Disease and Paget-like Lesions

Vulvar Paget disease typically presents as an eczematoid, red, weeping area on the vulva, often localized to the labia majora, perineal body, clitoral area, or other sites. This disease typically occurs in older, postmenopausal Caucasian women and may be associated with an underlying primary adenocarcinoma. Invasive Paget disease 1 mm or less in depth of invasion has reportedly little risk for recurrence.

Vulvar Malignant Melanoma

Malignant melanoma of the vulva accounts for approximately 9% of all primary malignant neoplasms on the vulva, and vulvar melanoma accounts for approximately 3% of all melanomas in women. This tumor occurs predominantly in Caucasian women, and the mean age at diagnosis is 55 years of age. Although usually pigmented, approximately one fourth are nonpigmented, amelanotic melanomas.

The level of invasion and tumor thickness are essential measurements in evaluating malignant melanoma. Malignant melanomas that have a thickness of less than 0.75 mm have little or no risk for metastasis and tumors up to 1 mm in thickness are generally considered to have minimal risk of recurrence. Melanomas of 1.49 mm thickness or less also correlate with good prognosis. A poor prognosis is correlated with thickness greater than 2 mm, or mitotic count exceeding 10/mm². Other poor prognostic factors include a minimal or nil inflammatory reaction and surface ulceration.

Metastatic Tumors to the Vulva

Most metastatic tumors to the vulva involve the labia majora or Bartholin gland. Metastatic tumors account for approximately 8% of all vulvar

tumors and in approximately one half of the cases, the primary tumor was in the lower genital tract, including the cervix, vagina, endometrium, and ovary. In approximately 10% of the cases, the primary site of the metastatic tumor cannot be identified.

PROGNOSTIC FACTORS

Prognosis has been most extensively evaluated in women with squamous cell carcinomas. The major prognostic factors in vulvar cancer—tumor diameter, depth of tumor invasion, nodal spread, and distant metastasis—have been incorporated into the current FIGO staging system. Risk of local recurrence, although clearly associated with tumor size and extent, is also related to the adequacy of the surgical resection margins. Several retrospective studies have confirmed an increased incidence of local recurrence in patients with microscopic margins less than 8 mm in formalin-fixed tissue specimens.

The single most important prognostic factor in women with vulvar cancer is metastasis to the inguinal lymph nodes, and most recurrences will occur within 2 years of primary treatment. The presence of inguinal node metastasis portends a 50% reduction in long-term survival. Because the clinical prediction of lymph node spread is inaccurate, node status is best determined via surgical biopsy. Prognostic issues that appear to be important in evaluating lymphatic involvement are (i) whether nodal spread is bilateral or unilateral, (ii) the number of positive nodes, (iii) the volume of tumor in the metastasis, and (iv) the level of the metastatic disease. Multiple positive nodes, bilateral metastases, involvement beyond the groin, and bulky disease are associated with poor prognosis.

TREATMENT

KEY POINTS

- Treatment should be individualized based on lesion location.
- Partial radical vulvectomy with inguinal lymphadenectomy through separate incisions is the treatment of choice for stage IB and some stage II tumors.
- Combined chemotherapy and radiation therapy is indicated for more advanced lesions that involve vital structures.
- Postoperative inguinal and pelvic irradiations are indicated for most patients with positive nodes.

The development of the radical vulvectomy with bilateral inguinofemoral lymphadenectomy during the 1940s and 1950s was a dramatic improvement over prior surgical options and greatly enhanced survival, particularly for women with smaller tumors and negative lymph nodes. Long-term survival of 85% to 90% can now be routinely obtained with radical surgery. However, radical surgery can be associated with postoperative complications such as disfigurement, wound breakdown, and lymphedema.

More recently, surgical emphasis has evolved to an individualized approach for tumors at either end of the spectrum. Many gynecologists believe that smaller vulvar tumors can be acceptably managed by less radical surgical approaches and have proposed more limited resections for certain subsets considered to represent early- or low-risk disease. The obvious advantages of such an approach are retention of a significant portion of the uninvolved vulva, less operative morbidity, and fewer late complications. In contrast, radical surgery is frequently ineffective in curing patients with bulky tumors or positive groin nodes. Multimodality programs that incorporate radiation, surgery, and chemotherapy are now being investigated in women with these high-risk tumors based upon success with similar approaches in women with squamous cancers of the cervix.

Microinvasive Tumors

Tumors demonstrating early invasion of the vulvar stroma (≤ 1 mm) have minimal risk for lymphatic dissemination. Excisional procedures that incorporate a 1-cm normal tissue margin are likely to provide a curative result. Patients in this category represent the only subset for whom evaluation of the groin lymph nodes is unnecessary. After primary therapy, these patients should undergo frequent follow-up examinations.

Stage I and II Cancers

Traditional management of stage I and II vulvar cancers has been radical vulvectomy with bilateral inguinofemoral lymphadenectomy. The operation removes the primary tumor with a wide margin of normal skin, along with the remaining vulva, dermal lymphatics, and regional nodes. This approach provides excellent long-term survival and local control in approximately 90% of patients. Disadvantages of radical surgery include the loss of normal vulvar tissue with alterations in appearance and sexual function, a 50% incidence of wound breakdown, a 30% incidence of groin complications (breakdown, lymphocyst, and lymphangitis), and a 10% to 15% incidence of lower extremity lymphedema. Additional postoperative therapy, primarily irradiation, should be considered in the 10% to 20% of patients with positive nodes with the understanding that this will further increase the incidence of lymphedema.

In an effort to reduce morbidity and enhance psychosexual recovery, several groups have espoused a more limited surgical approach for women with small vulvar cancers. The most frequent recommendation is to resect the primary lesion with a 1- to 2-cm margin of normal tissue and to carry the dissection to the deep perineal fascia. This partial radical vulvectomy should not be confused with the concept of excisional biopsy, which is used primarily as a diagnostic procedure.

Limited resection of the primary tumor is combined with a more conservative surgical approach to the groin, in which the ipsilateral groin nodes are used as the sentinel group for lymphatic metastases. Bilateral dissections are performed in patients whose tumors encroach on midline structures (clitoris or perineal body). In patients with negative inguinal nodes, no further dissection or postoperative therapy is used. Patients with

positive nodes can undergo additional nodal dissection of the contralateral groin or be treated with postoperative irradiation, or both. Patients with deep lymphadenectomy followed by irradiation have the greatest likelihood of lymphedema.

With limited resection, survival of 90% or better is attainable for patients with stage I vulva carcinoma with acceptable anatomic appearance and function. In an attempt to reduce treatment-related morbidity, the classic radical operation has been replaced by the use of “triple incision” techniques that separate the vulvectomy incision from the groin incisions.

Another surgical concept, which is undergoing evaluation is the potential for cutaneous lymphatic mapping to define and target the true sentinel groin nodes. Preliminary experience with both intraoperative lymphatic dye and radioisotope injections suggests that a sentinel node can often be identified in the groin. This early experience supports the concept that the assessment of lymphatic metastases may ultimately be reduced to the biopsy of 1 or 2 identifiable nodes.

In summary, therapy for women with stage I and II cancers must be individualized to the patient and her tumor. Radical vulvectomy provides excellent local control and long-term survival, but has significant morbidity and sexual function limitations. More conservative approaches appear safe in most stage I settings and may be applicable in some stage II patients. The surgical approach to the groin nodes is evolving. The accuracy of the “sentinel” node identified by intraoperative mapping as predictors of nodal spread is currently being evaluated. If these concepts prove suitably sensitive and specific, more extensive inguinal lymphadenectomy might be abandoned.

Stage III and IV Cancers

By definition, stage III tumors extend to adjacent mucosal structures or the inguinal lymph nodes. Many are bulky, but some are of limited volume but considered high stage because of proximity to critical central structures. Some of these primary tumors can be curatively resected by radical operations, such as radical vulvectomy or some variation of pelvic exenteration and vulvectomy. Recent therapeutic efforts have focused on combined modality treatment programs involving sequenced radiation therapy or chemoradiation therapy and radical surgery. There are now ample data from retrospective series, and a few prospective trials, from which to conclude that vulvar cancers are radioresponsive and that function-sparing operations are feasible in selected patients with advanced disease who receive combined modality treatment. A similar experience has been reported for patients with stage IVA tumors. Ultraradical (exenteration) resection may also be considered for selected patients.

Node Positive Cancers

Patients who undergo bilateral inguinofemoral lymphadenectomy as initial therapy and are found to have positive nodes—particularly more than one positive node—are likely to benefit from postoperative irradiation to the groins and lower pelvis. Radiation therapy is superior to surgery in the

TABLE 5.3

**UNANTICIPATED GROIN FAILURE IN PATIENTS WITH
NEGATIVE SUPERFICIAL LYMPHADENECTOMY**

Investigators	No.	%
Burke et al.	4/76	5.2
Berman et al.	0/50	0
Stehman et al.	6/121	5.0
Gordinier	9/104	8.6
Total	19/351	5.4

Source: Adapted from Moore DH, Koh WJ, McGuire WP, Wilkinson EJ. Chapter 20: Vagina. In: *Principles and Practices of Gynecologic Oncology*, 5th Ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009:572.

management of patients with positive pelvic nodes. Several management options are available for patients found to have positive nodes; however, if postoperative radiotherapy to the inguinal nodes is deemed necessary, it would be reasonable to limit resection to grossly positive nodes. Excellent local control and minimal morbidity have been achieved when selective inguinal lymphadenectomy and tailored postoperative adjuvant therapy were administered to carefully selected patients.

Recurrent Cancer

Regardless of initial treatment, vulvar cancer recurrences can be categorized into three clinical groups: local (vulva), groin, and distant. The reported experience with local recurrence on the vulva is surprisingly good. Recurrence-free survival can be obtained in up to 75% of cases when the recurrence is limited to the vulva and can be resected with a gross clinical margin. Recurrences in the groin have, in the past, been deemed to be universally fatal; however, a few patients may be salvaged by combined modality therapy utilizing chemoradiation $\pm$ surgical resection of residual bulky disease (Table 5.3). Patients who develop distant metastases are candidates for systemic cytotoxic therapy, which is largely palliative.

SURGICAL TECHNIQUES

Radical Vulvectomy and Bilateral Inguinofemoral Lymphadenectomy

The traditional incisions for radical vulvectomy and bilateral lymphadenectomy described as a “butterfly” or “longhorn” approach have largely been abandoned.

Radical Wide Excision

In procedures used to resect small vulvar cancers, incisions are devised to allow for at least a 2-cm resection margin encompassing the primary lesion (Fig. 5.2). Dissection is carried to the deep perineal fascia. Recent data suggest that a 1-cm margin may be adequate for some tumors. Most radical wide excision sites can be closed primarily. Some form of inguinal lymphadenectomy, performed through a separate incision, is generally combined with radical wide excision. The necessary extent of the groin dissection is an area of current investigation. Wound breakdown, usually of minor degree, is reported in approximately 15% of cases.

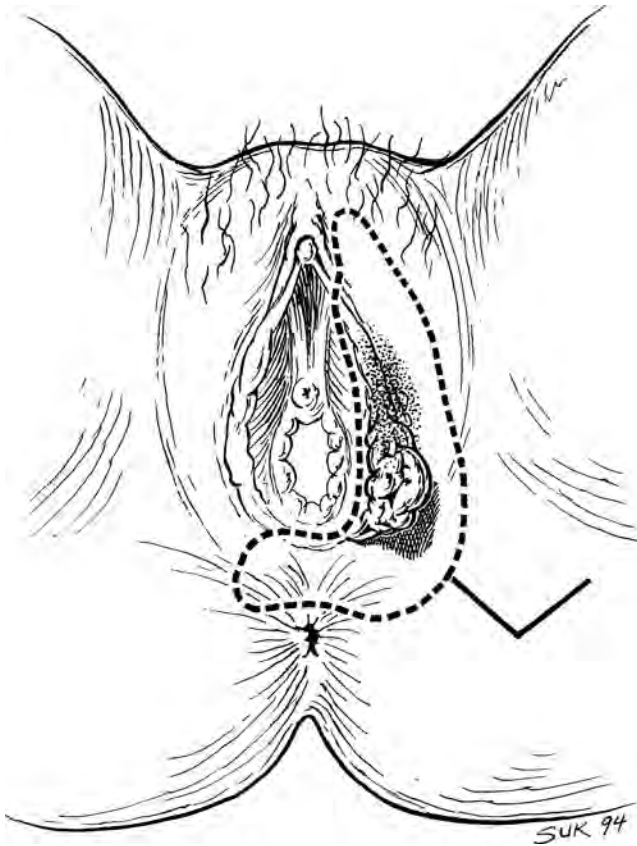


FIGURE 5.2. Planned resection of a left labial squamous carcinoma and adjacent carcinoma *in situ* by radical wide excision. A 2-cm margin is outlined. Rhomboid-flap repair using a V-incision is anticipated.

Source: Reprinted from Burke TW, Morris M, Levenback C, et al. Closure of complex vulvar defects using local rhomboid flaps. *Obstet Gynecol.* 1994;84:1044.

Triple Incision Techniques

This resection allows complete removal of the vulvar skin in a manner identical to that achieved with radical vulvectomy; however, bilateral inguinofemoral lymphadenectomy is accomplished via separate incisions parallel to the inguinal ligaments. The three incision concept preserves the radicality of the vulvar resection while retaining skin over the groin and the incidence of major wound breakdown is reduced.

Management of the Groin

Excisional Biopsy

Most preoperative diagnostic dilemmas related to enlarged groin nodes can be resolved simply and accurately using fine needle aspiration biopsy. However, selective excision of groin lymph nodes may be considered when fine needle aspiration biopsy results are negative or equivocal, or to remove bulky positive nodes before beginning a course of combined modality therapy.

Superficial Inguinal Lymphadenectomy

Superficial inguinal lymphadenectomy involves the removal of the eight to ten lymph nodes that lie superficial to the cribriform fascia and surrounding the branches of the saphenous vein. This is a more meticulous and complete lymphatic dissection than that described for excisional biopsy.

Deep Inguinal (Femoral) Lymphadenectomy

The deep inguinal (femoral) lymph nodes lie medial to the femoral vein beneath the cribriform fascia. This space contains three to five nodes, the channels of which course beneath the inguinal ligament and continue in the pelvis as the external iliac nodal chain. The most superior deep inguinal node is known as Cloquet node.

Surgical removal of the deep nodes is performed as an extension of a superficial lymphadenectomy rather than as an isolated procedure. The usual approach is to open the cribriform fascia along the sartorius muscle at the time of the superficial lymphadenectomy. Because all of the deep nodes are consistently located medial to the femoral vein, some surgeons have recommended eliminating the removal of the entire cribriform plate.

Sentinel Lymph Node Mapping and Biopsy

The concept of a “sentinel lymph node” suggests that the sentinel lymph node is the first lymph node in the lymphatic pathway and the main site of metastasis. The use of an intraoperative blue dye staining technique along with lymphoscintigraphy using radioactive ^{99m}Tc administered shortly before surgery, combined with the intraoperative use of a hand-held gamma probe, produces the highest sensitivity of sentinel lymph node identification.

Because sentinel lymph nodes are subjected to a more rigorous pathologic (ultrastaging) examination, sentinel lymph node biopsy can allow for the detection of smaller tumor foci compared to complete groin node dissection and traditional pathologic examination. Factors that may contribute to the failure of sentinel lymph node identification include the following: midline location for the primary tumor and stasis of lymph flow from a node completely replaced by tumor. The prognosis associated with groin relapse is poor, and sentinel lymph node identification and biopsy should be confirmed by a prospective randomized controlled trial before sentinel lymph node identification and biopsy may be considered part of the standard of surgical care for vulva carcinoma.

Surgical Resection for Recurrent Disease

The site, extent, and volume of recurrent vulvar cancer have important implications on both resectability and potential for cure. Surgical therapy plays a curative or palliative role in selected subsets of patients with recurrent disease.

Radical Wide Excision

As many as 75% of patients with recurrent disease limited to the vulva can be salvaged by radical wide excision or re-excision of the tumor. Surgical principles of recurrent vulva tumors are identical to those for primary tumors: wide excision with a measured normal tissue margin of at least 2 cm. Particular attention is also focused on obtaining a clear deep margin.

Pelvic Exenteration

Selected patients have achieved long-term survival after pelvic exenteration for vulvar recurrences extending to the vagina, proximal urethra, or anus. The surgical approach in these cases should be individualized to the size and location of the recurrent tumor, prior therapies, and the age and overall health of the patient. Patients considered for pelvic exenteration should have a thorough preoperative evaluation to exclude the presence of regional and/or distant metastases.

Resection of Groin Recurrence

Surgical resection should be viewed with caution in the previously irradiated patient. Cure is unlikely with resection alone, and wound healing is impaired. The debility caused by a combination of unresolved recurrence and surgical wound breakdown is worse than that of progressive recurrence alone. Patients who develop groin recurrence without a history of prior irradiation should be considered for surgical resection in combination with preoperative or postoperative radiation therapy $\pm$ concurrent chemotherapy. Isolated groin recurrence is a rare event, so the data to support the efficacy of this treatment are anecdotal.

RADIATION THERAPY

Treating Locally Advanced Disease in the Vulva

Following initial resection of a vulvar primary, various surgico-pathologic features have been identified that are associated with a higher risk of local recurrence. Tumor size, nodal status, margin status (<8 mm), lymphovascular space invasion, and deep tumor penetration have all been associated with an increased risk of recurrence. Although many local recurrences are controlled with additional surgery or irradiation, salvage surgery is often morbid, and local recurrences may provide additional opportunity for regional and distant tumor spread. While no prospective trials of post-operative vulvar site radiotherapy have been completed, adjuvant radiation of the primary tumor bed in selected patients with close margins or other high-risk features does improve local tumor control.

Alternatively, in patients who present with more advanced primary tumors, radiation therapy may be delivered preoperatively. Several investigators have reported excellent responses and high local control rates after preoperative treatment of advanced tumors with relatively modest doses of radiation therapy followed by local resection. More recently, a number of published series have suggested the therapeutic benefit of concurrent chemoradiation, typically followed by limited surgical resection, in addressing locally advanced disease (Table 5.4). Randomized trials of the role of chemoradiation have not been done in vulvar cancer. However, recent trials that demonstrated improved local control and survival when

TABLE 5.4
CONCURRENT CHEMOIRRADIATION IN THE MANAGEMENT OF LOCALLY ADVANCED OR RECURRENT CARCINOMA OF THE VULVA

Investigators	No.	Chemotherapy	RT Dose (Gy)	No. with Recurrent or Persistent Local Disease After RT Surgery	Follow-up (months)
Moore	73	5-FU + CDDP	47.6	15 (21%)	22–72
Landoni	58	5-FU + Mito	54	13 (22%)	4–48
Lupi	31	5-FU + Mito	54	7 (23%)	22–73
Scheistroen and Trope	42	Bleomycin	45	39 (93%)	7–60

5-FU, 5-fluorouracil; Mito, mitomycin C; CDDP, cisplatin; RT, radiation therapy.
Source: Adapted from Moore DH, Koh WJ, McGuire WP, Wilkinson EJ. Chapter 20: Vagina. In: *Principles and Practices of Gynecologic Oncology*, 5th Ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009:578.

concurrent cisplatin-containing chemotherapy was added to radiation treatment of cervical cancers suggest that this approach may also be useful for women with other locally advanced lower genital tract neoplasms.

The most compelling data in support of concurrent chemoradiation in the management of locally advanced disease come from a large prospective phase II trial performed by the Gynecologic Oncologic Group (GOG protocol 101). In this study, 71 evaluable patients with locally advanced T3 or T4 disease who were deemed not resectable by standard radical vulvectomy underwent preoperative chemoradiation. Chemotherapy consisted of two cycles of 5-fluorouracil and cisplatin. Radiation was delivered to a dose of 47.6 Gy, using a planned split-course regimen, with part of the radiation given twice daily during the 5-fluorouracil infusion. Patients underwent planned resection of the residual vulvar tumor, or incisional biopsy of the original tumor site in the case of complete clinical response, 4 to 8 weeks after chemoradiotherapy. A complete clinical tumor response was noted in 33/71 (47%) patients. Following vulvar excision or biopsy, 22 patients (31%) were found to have no residual tumor in the pathologic specimen. With a median follow-up interval of 50 months, 11 patients (16%) have developed locally recurrent disease in the vulva.

Treatment of Regional Disease

Although radical inguinal lymphadenectomy has historically been considered the treatment of choice for regional management of invasive vulvar carcinoma, a number of retrospective studies have suggested that regional prophylactic radiation therapy is an effective method of preventing groin recurrences with minimal morbidity. The Gynecologic Oncology Group tried to define the optimal approach to clinically negative inguinal nodes in a trial that randomized patients between inguinal node irradiation and radical lymphadenectomy (followed by inguinopelvic irradiation in patients with positive nodes) after resection of the primary tumor. This study was closed after entry of only 58 patients when there appeared to be a higher rate of groin recurrence in the radiation treatment arm. However, this study has been criticized because the treatment protocol was not CT-based, recommended combination photon and electron dosing to a depth of 3 to 4 cm, and likely delivered an inadequate dose to the inguinal nodes.

While the role of prophylactic radiotherapy in the undissected but high-risk groin remains controversial, there is strong evidence that adjunctive radiation therapy improves regional tumor control and survival in patients who have documented nodal metastases following inguinal node dissection. The critical role of radiation therapy was not appreciated until 1986, when results of a prospective Gynecologic Oncology Group trial in 114 patients with inguinal metastases were published. In that study, all patients underwent radical vulvectomy and inguinal lymphadenectomy. Patients who had positive inguinal nodes were randomized intraoperatively to receive either pelvic node dissection or postoperative irradiation to the pelvis and inguinal nodes. This trial was closed before the projected accrual goal because an interim analysis revealed a statistically significant overall survival advantage for the radiation treatment arm ($p = 0.03$). The

differences between the 2-year survival rates of patients treated with radiation therapy or pelvic dissection were most marked for patients presenting with clinically positive nodes (59% and 31%, respectively) and for those with two or more positive groin nodes (63% and 37%, respectively). There was no significant difference in survival between the treatment groups for patients with only one microscopically positive node, although the authors commented that the number of patients in this subset was insufficient for reliable analysis. The most striking difference in the patterns of recurrence for the two treatment groups was the much larger number of inguinal failures among patients who were treated with surgery alone (Fig. 5.3). These groin recurrences were rarely if ever salvageable. The vulva, regardless of tumor pathologic risk factors, was not included in the radiation treatment fields in this study, and approximately 9% of patients in both treatment arms had recurrences at the primary site at the time of the analysis, raising the question of whether selective radiation to the vulva may have decreased local recurrences. The role of adjuvant radiation for patients with a single positive groin node following inguinal node dissection remains unresolved.

Successful use of concurrent chemotherapy and radiation therapy following radical hysterectomy in cervical cancer patients with positive lymph nodes suggests that concurrent chemoradiotherapy might be valuable for patients with node positive vulvar cancer.

However, the role of preoperative chemoradiation has been assessed in patients who present with bulky, unresectable inguinal adenopathy. In the GOG 101 study of preoperative chemoradiation for local regionally advanced vulvar cancer, there was a cohort of 42 evaluable patients with N_2 or N_3 nodal disease that were deemed initially unresectable. In only two patients (5%) did nodal disease remain unresectable after combined

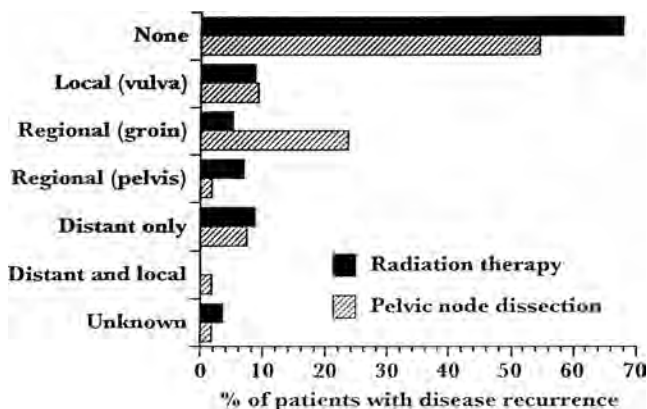


FIGURE 5.3. Sites of disease recurrence in patients treated with adjuvant radiation therapy to the pelvis and inguinal region or with pelvic node dissection following radical vulvectomy and bilateral inguinal lymphadenectomy.

Source: Modified from Homesley HD, Bundy BN, Sedlis A, et al. Radiation therapy versus pelvic node resection for carcinoma of the vulva with positive groin nodes. *Obstet Gynecol.* 1986;68:733.

chemotherapy and radiation therapy. The surgical specimen showed histologic clearance of nodal disease in 15 patients (36%). At a median follow-up of 78 months only, 1/37 (3%) patients relapsed in the groin. This study, while nonrandomized, provides further evidence of the efficacy of combined chemoradiotherapy in the management of locally regionally advanced vulvar cancer and in patients with significant regional adenopathy. Given the high risk of distant relapse with node positive vulvar cancer, especially in those with greater than or equal to two involved nodes, it seems reasonable to consider adjuvant chemoradiation for such high-risk patients.

Radiation Therapy Technique

Techniques commonly used for the treatment of vulvar carcinoma reflect the need to encompass the lower pelvic and inguinal nodes as well as the vulva while minimizing the dose to the femoral heads. One approach is to treat with an anterior field that encompasses the inguinal regions, lower pelvic nodes, and vulva and a narrower posterior field that encompasses the lower pelvic nodes and vulva but excludes the majority of the femoral heads. CT scans are used to determine the appropriate electron energy and to detect enlarged nodes that may not be appreciated on clinical exam. Gross disease in the groins or vulva may be boosted with *en face* electron fields. In some cases, interstitial implants or *en face* electron fields may be used to boost the dose to the primary site. If radiation is directed to the regional nodes only, with intentional sparing of the vulva, care must be taken to avoid a large “midline” block, which may lead to higher medial groin and vulvar failures.

The complex anatomy of the vulva and its regional lymphatics, interwoven with adjacent critical normal tissues, has led some investigators to propose the use of intensity modulated radiation therapy in the management of vulvar cancer.

Acute Complications of Radiation Therapy

Acute radiation reactions are brisk, and doses of 35 to 45 Gy routinely induce confluent moist desquamation. However, with adequate local care, this acute reaction usually heals within 3 to 4 weeks. Sitz baths, steroid cream, and treatment of possible superimposed *Candida* infection all help to minimize the discomfort. If the patient is sufficiently flexible, she may be placed in a frog-leg position during treatment to minimize the dose and ensuing skin reaction on the medial thighs; care must then be taken, however, to deliver an adequate dose to the vulvar skin. Although most patients will develop confluent mucositis by the fourth week of treatment, this is usually tolerated if the patient is warned in advance and assured that the discomfort will resolve after treatment is completed. Although a treatment break is occasionally required, delays should be minimized, because they may allow time for the repopulation of tumor cells.

Late Complications of Radiation Therapy

Many factors add to the late morbidity of radiation treatment in patients with vulvar carcinoma. Patients with advanced vulvar carcinomas often

are treated with radiation therapy following radical surgery, which may include extensive dissection of the inguinal and possibly pelvic nodes. Large ulcerative cutaneous lesions frequently have superimposed infection. Patients are often elderly and may have complicating medical conditions, such as diabetes, multiple prior surgeries, and osteoporosis. The contribution of concurrent chemotherapy to local morbidity is not yet clearly defined, but may contribute to bowel and bone complications.

The incidence of lower extremity edema after inguinal irradiation alone is negligible. Although radiation therapy probably contributes to the incidence of peripheral edema following radical node dissection, no difference was evident in a GOG randomized study. In general, with careful treatment planning technique, the risk of major late complication following regional nodal radiation, either electively or adjuvant to lymph node dissection, is low.

CHEMOTHERAPY

Squamous Cell Carcinoma

Squamous carcinoma is the only cell type for which reproducible information exists on the value of cytotoxic therapy. Several drugs have undergone Phase II testing in squamous vulvar cancer. Only doxorubicin and bleomycin appear to have activity as single agents. Cisplatin has notably little activity in vulvar and vaginal squamous tumors. This lack of activity, however, is based on the treatment of refractory patients only. No trials of this agent as a presurgical cytoreductive regimen have been attempted. With the recent dramatic results obtained with concurrent cisplatin-based chemotherapy and radiation therapy in locally advanced squamous cancer

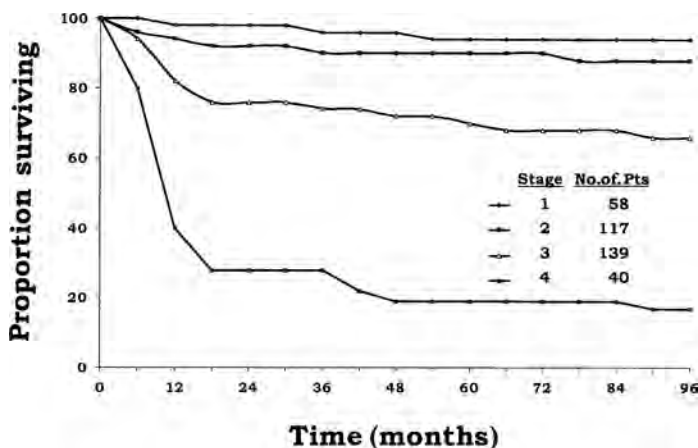


FIGURE 5.4. Invasive squamous vulvar carcinoma. Survival by FIGO stage.
Source: Patients treated at M. D. Anderson Cancer Center 1944–1990; data courtesy of F. N. Rutledge.

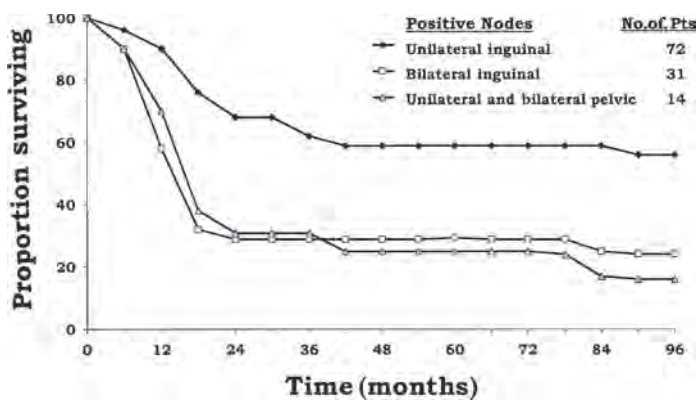


FIGURE 5.5. Invasive squamous vulvar carcinoma. Survival of patients with positive nodes.
Source: Data courtesy of F. N. Rutledge.

of the cervix, one must consider a similar approach in the patient with locally advanced squamous cancer of the vulva. Several drug combinations have also been used in squamous vulvar cancer. Toxicity with these regimens has been reported as tolerable.

There are some increasing reports of the concomitant use of cytotoxic therapy with irradiation, usually as primary therapy in advanced and inoperable disease. The largest experience in vulvar cancer was recently reported by the Gynecologic Oncology Group, and is noted above.

RESULTS OF THERAPY

The overall results of therapy for women with squamous cancers of the vulva are excellent. Approximately two thirds of patients present with early-stage tumors. Five-year survival rates of 80% to 90% are routinely reported for stage I and II diseases. As anticipated, survival rates for patients with advanced disease are poor: 60% for stage III cases and 15% for stage IV (Fig. 5.4). The survival rate for women with nodal spread is one-half that of women without nodal disease who have similarly sized primary tumors (Fig. 5.5).

MANAGEMENT OF OTHER VULVAR MALIGNANCIES

Malignant Melanoma

Malignant melanoma is the second most common vulvar malignancy. The primary treatment modality for vulvar melanoma is radical surgical excision. Because most failures are distant, ultraradical local resection does

not appear to enhance survival. Depth of invasion and the presence of ulceration are significant prognostic factors, and should be considered in treatment planning. Look et al. reported that none of the patients with lesion depth of less than or equal to 1.75 mm experienced a recurrence, and suggested that these patients could be treated with wide local excision. In contrast, all patients with lesion depth of greater than 1.75 mm recurred despite radical tumor excision. Lymphadenectomy can be avoided in patients with superficial melanomas for whom the risk of metastatic disease is negligible. Sentinel lymph node identification and biopsy may have a role, although data regarding sentinel lymph node biopsy for vulvar melanomas are limited. Radiation therapy may be useful in enhancing local and regional control for some high-risk patients.

Systemic chemotherapy, in either an adjuvant or salvage setting, is considered palliative but responses are truly rare and adverse effects may be significant. Biologic and immunologic approaches to the treatment of malignant melanoma are currently being evaluated.

Overall survival rates in women with vulvar melanoma are approximately 50%. Patients with superficial lesions have an excellent chance for cure after surgical resection, but patients with deeper lesions or metastases at the time of diagnosis have a more limited prognosis.

Verrucous Carcinoma

Verrucous carcinomas are locally invasive and rarely metastasize. Consequently, treatment by radical wide excision is usually curative. Local recurrence can occur, especially when the tumor has been inadequately resected.

Basal Cell Carcinoma

Basal cell carcinomas should be removed by excisional biopsy using a minimum surgical margin of 1 cm. Lymphatic or distant spread is exceedingly rare.

Adenocarcinoma

Despite the paucity of data regarding the evaluation and treatment of vulva adenocarcinoma, resection of localized disease by radical wide excision, hemivulvectomy, or radical vulvectomy seems appropriate. The incidence of groin node metastases is approximately 30%. Some form of inguinal lymphadenectomy should be included with primary surgical resection. Radiation therapy may have a role in enhancing local control for women with large primary tumors or inguinal metastases.

Paget Disease

Paget disease should be resected with a wide margin, but recurrences are common. If underlying invasion is suspected, the deep margins should be

extended to the perineal fascia. Repeat local excision of recurrent disease is usually effective in the absence of invasion.

Vulvar Sarcomas

All types of vulva sarcoma are rare, but leiomyosarcoma, malignant fibrous histiocytoma, and rhabdomyosarcoma predominate. Cures have occasionally been obtained with aggressive resection of either primary or locally recurrent disease. The results of regional and systemic therapy for leiomyosarcoma are disappointing; however, rhabdomyosarcoma seems to be more responsive to both chemotherapy and radiation than other soft tissue sarcomas. The current treatment of choice is to combine chemoradiation with limited surgical resection of residual disease.

FUTURE DIRECTIONS

Vulvar cancer is an uncommon neoplastic disease and its relative rarity is a major obstacle in designing prospective randomized trials. Current trends in its management are focusing on a more individualized approach

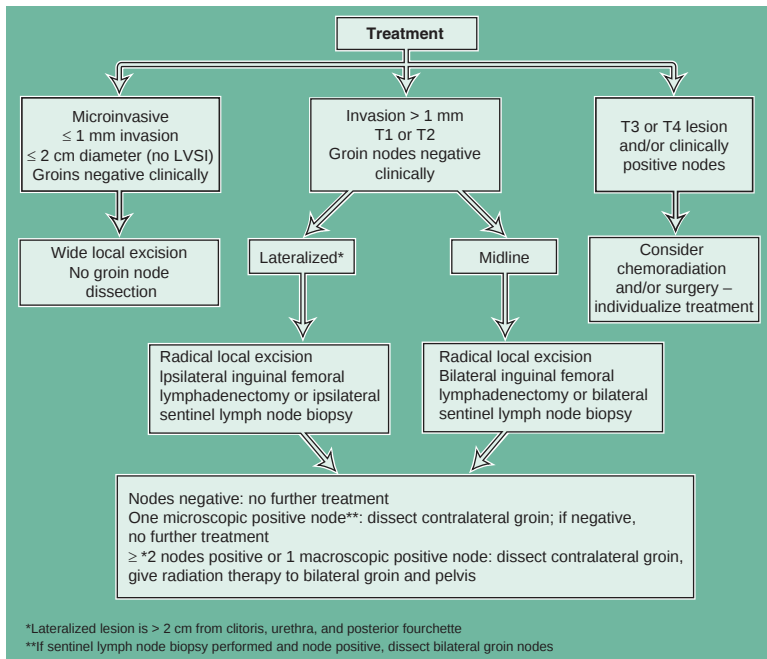


FIGURE 5.6. Management of invasive vulvar cancer.

Source: Markman M, ed. *Atlas of Cancer*. 2nd Ed. Philadelphia, PA: Springer; 2008.

that emphasizes conservative vulva surgical resection when feasible, the use of reconstructive procedures to preserve or restore vulva function, potential reduction in groin complications through sentinel lymph node biopsy, and multimodality therapy for advanced or disseminated disease (Fig. 5.6).

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CHAPTER 6 ■ THE VAGINA

ANATOMY

The vagina is a muscular dilatable tubular structure averaging 7.5 cm in length that extends from the cervix to the vulva. It lies dorsal to the bladder and urethra, and ventral to the rectum. The upper portion of the posterior wall is separated from the rectum by a reflection of peritoneum, the pouch of Douglas. The vaginal wall is composed of three layers: the mucosa, muscularis and adventitia. The inner mucosal layer is formed by a thick, nonkeratinizing, stratified squamous epithelium.

The lymphatics in the upper portion of the vagina drain primarily via the lymphatics of the cervix; the upper anterior vagina drains along cervical channels to the interiliac and parametrial nodes; the posterior vagina drains into the inferior gluteal, presacral, and anorectal nodes. The distal vaginal lymphatics follow drainage patterns of the vulva into the inguinal and femoral nodes and from there to the pelvic nodes. Bilateral pelvic nodes should be considered to be at risk in any invasive vaginal carcinoma, and bilateral groin nodes should be considered to be at risk in those lesions involving the distal third of the vagina.

EPIDEMIOLOGY AND ETIOLOGIC RISK FACTORS

KEY POINTS

- Eighty-ninety percent of vaginal neoplasms represent metastasis from other primary gynecologic (cervix or vulva) sites, involving the vagina by direct extension or lymphatic routes.
- Peak incidence of vaginal carcinoma is in the sixth and seventh decades of life; however, it is increasingly seen in younger women, possibly due to human papillomavirus infection.

Primary vaginal cancer, defined as a lesion arising in the vagina without involvement of the cervix or vulva, is a rare entity, representing only 1% to 2% of all female genital neoplasias. Most vaginal neoplasms, 80% to 90%, represent metastasis from other primary gynecologic (cervix or vulva) and nongynecologic sites, involving the vagina by direct extension or lymphatic or hematogenous routes.

Carcinoma of the vagina is considered to be associated with advanced age, with the peak incidence occurring in the sixth and seventh decades of life. However, vaginal cancer is increasingly being seen in younger women, possibly due to human papillomavirus (HPV) infection or other sexually transmitted diseases. Only about 10% of patients are 40 years of age or younger. A decrease in the incidence of primary vaginal tumors has been noted in recent years, possibly because of early detection with cervical cytology or more rigid diagnostic criteria, which have eliminated from this category primary cancers arising from adjacent organs, such as the cervix, vulva, or endometrium.

Vaginal Intraepithelial Neoplasia and Squamous Cell Carcinoma

Potential risk factors for squamous cell carcinoma (SCC) include prior history of HPV infection, cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), immunosuppression, and possibly previous pelvic irradiation. HPV is the likely etiologic agent of SCC and its precursor lesion, vaginal intraepithelial neoplasia (VAIN).

In studies reporting on groups of women with VAIN and SCC of the vagina, the following risk factors have been identified: five or more sexual partners, sexual debut before age 17 years, smoking, low socioeconomic status, a history of genital warts, prior abnormal cytology, and prior hysterectomy. There is also evidence that *in utero* exposure to diethylstilbestrol (DES) doubles the risk of development of VAIN. The putative mechanism is an enlargement of the transformation zone at risk, which is then at risk for infection with HPV.

Patients with previous cervical carcinoma have a substantial risk of developing vaginal carcinoma, presumably because these sites share exposure and/or susceptibility to endogenous or exogenous carcinogenic stimuli. About 10% to 50% of patients with VAIN-carcinoma *in situ* (CIS) or invasive carcinoma of the vagina have undergone prior hysterectomy or radiotherapy (RT) for CIS or invasive carcinoma of the cervix. The interval from therapy for cervical cancer or preinvasive disease to the development of carcinoma of the vagina averages nearly 14 years.

Clear Cell Adenocarcinoma

An increased incidence of clear cell adenocarcinoma (CCA) of the vagina in young women related to *in utero* exposure to DES during the first 16 weeks of pregnancy was first reported in 1971. Specific suggested mechanisms of carcinogenesis focus on the retention of nests of abnormal cells of müllerian duct origin, which, after stimulation by endogenous hormones during puberty, are promoted into adenocarcinomas. The median age at diagnosis in the DES-exposed patients is 19 years, whereas prior to this report, most patients with CCA of the vagina were elderly. Hicks and Piver noted that 60% of CCA patients had been exposed to DES or similar agents *in utero*, that most cases involved the anterior upper third of the vaginal

wall, and that DES-associated CCA cases had been reported from ages 7 to 34 (median, 19 years). Fortunately, the incidence of this tumor has decreased in recent years, and may decrease even more since the practice of prescribing DES during pregnancy has been discontinued.

Melanoma

Malignant melanoma is the second most common cancer of the vagina, accounting for 2.8% to 5% of all vaginal neoplasms. The most common location is the lower third and the anterior vaginal wall, although often-times it is multifocal.

Sarcomas

Sarcomas represent 3% of primary vaginal cancers, and are most common in adults, with leiomyosarcoma representing 50% to 65% of vaginal sarcomas. Malignant mixed müllerian tumor (MMMT, carcinosarcoma), endometrial stromal sarcoma, and angiosarcoma are less common. Embryonal rhabdomyosarcoma (RMS)/sarcoma botryoides is a rare pediatric tumor. Prior pelvic RT is a risk factor, particularly for mixed mesodermal tumors and vaginal angiosarcomas. Histopathologic grade appears to be the most important predictor of outcome.

NATURAL HISTORY

KEY POINTS

- The majority of vaginal primaries occur in the upper third or at the apex of the vault, most commonly in the posterior wall.
- If positive biopsies of the cervix or the vulva return at the time of initial diagnosis, the tumor cannot be considered to be a primary vaginal lesion.
- There is a significant risk of nodal metastasis for patients with disease beyond stage I.

The majority (57% to 83%) of vaginal primaries occur in the upper third or at the apex of the vault, most commonly in the posterior wall; the lower third may be involved in as many as 31% of patients. Lesions confined to the middle third of the vagina are uncommon. The location of the vaginal carcinoma is an important consideration in planning therapy and determining prognosis. Vaginal tumors may spread along the vaginal walls to involve the cervix or the vulva. However, if biopsies of the cervix or the vulva are positive at the time of initial diagnosis, the tumor cannot be considered a primary vaginal lesion. A lesion on the anterior wall may infiltrate the vesicovaginal septum and/or the urethra; those on the posterior wall may eventually involve the rectovaginal septum and subsequently infiltrate the

rectal mucosa. Lateral extension toward the parametrium and paracolpal tissues is not uncommon in more advanced stages of the disease.

There is a significant risk of nodal metastasis for patients with disease beyond stage I. Although data on staging lymphadenectomy are sparse, two studies reported a significant incidence of nodal disease in early-stage vaginal carcinoma. In the series by Al-Kurdis and Monaghan, the incidence of pelvic nodal metastasis was 14% and 32% for stages I and II, respectively, whereas in the series by Davis et al., the incidence was 6% and 26% for stages I and II, respectively. The incidence is expected to be higher for stage III, although no substantial data are available. The incidence of clinically positive inguinal nodes at diagnosis reported by several authors ranges from 5.3% to 20%.

Distant metastasis may occur, primarily in patients with advanced disease at presentation, or those who recurred after primary therapy. In the series by Perez et al. (1999), the incidence of distant metastasis was 16% in stage I, 31% in stage IIA, 46% in stage IIB, 62% in stage III, and 50% in stage IV.

CLINICAL PRESENTATION

Vaginal Intraepithelial Neoplasia—Carcinoma *In Situ*

VAIN most often is asymptomatic. In modern practice, VAIN is usually detected by cytologic evaluation performed following hysterectomy as part of a surveillance strategy in patients with a history of CIN or invasive cervical carcinoma. In these cases, VAIN has a predilection for involvement of the upper vagina; likely secondary to a “field effect.” It should be noted that evidence-based guidelines do not support routine cytologic studies following hysterectomy for noncervical pathology. Rather, surveillance cytology posthysterectomy should be limited to those patients with a prior history of CIN or invasive cervix cancer.

Invasive Squamous Cell Carcinoma

In patients with invasive disease, irregular vaginal bleeding, often postcoital, is the most common presenting symptom followed by vaginal discharge and dysuria. Pelvic pain is a relatively late symptom generally related to tumor extent beyond the vagina.

Other Histologies

The most common presenting symptom in patients with CCA is vaginal bleeding (50% to 75%) or abnormal discharge. More advanced cases may present with dysuria or pelvic pain.

Embryonal RMS, the most common malignant vaginal tumor in children, presents as a protruding, edematous grapelike mass. Ninety percent of these sarcomas present before the age of 5 years.

DIAGNOSTIC WORKUP

In general, in patients with suspected vaginal malignancy, thorough physical examination with detailed speculum inspection, digital palpation, colposcopic and cytologic evaluation, and biopsy constitutes the most effective procedure for diagnosing primary, metastatic, or recurrent carcinoma of the vagina. Examination under anesthesia is recommended for the thoroughness of evaluation of all of the vaginal walls and local extent of the disease, primarily if the patient is in great discomfort because of advanced disease, in order to obtain a biopsy. Biopsies of the cervix, if present, are recommended to rule out a primary cervical tumor. The speculum must be rotated as it is slowly withdrawn from the vaginal fornix so that the total vaginal mucosa may be visualized, and, in particular, posterior wall lesions, which occur frequently, are not overlooked.

The patient with a history of preinvasive or invasive carcinoma of the cervix found to have abnormal cytology following prior hysterectomy or RT should be offered vaginotomy with the application of acetic acid to the entire vault, followed by biopsies as indicated by areas of white epithelium (“aceto-white” areas), mosaicism, punctation, or atypical vascularity. Application of half-strength Schiller iodine following the application of acetic acid to determine if the Schiller-positive (non-staining) areas correspond with the aceto-white areas is another method of identifying high-risk regions requiring biopsy.

STAGING

At present, primary malignancies of the vagina are all staged clinically. In addition to a complete history and physical examination, routine laboratory evaluations including complete blood cell count with differential and platelets and assessment of renal and hepatic function should be undertaken. In order to determine the extent of disease, the following tests are allowed by International Federation of Gynecology and Obstetrics (FIGO) criteria: chest radiograph, a thorough bimanual and rectovaginal examination, cystoscopy, proctoscopy, and intravenous pyelogram. It can be difficult even for the experienced examiner to differentiate between disease confined to the mucosa (stage I) and disease spread to the submucosa (stage II).

Pelvic computed tomography (CT) scan is generally performed to evaluate inguino-femoral and/or pelvic lymph nodes, as well as extent of local disease. In patients with vaginal melanoma or sarcoma, chest, abdomen, and pelvic CT scans are often part of the workup. Magnetic resonance imaging (MRI) has emerged as a potentially important imaging modality in the evaluation of vaginal cancers, predominantly the T1-weighted images with contrast and T2-weighted images. Positron emission tomography (PET) is evolving as a modality of potential use in the evaluation of vaginal cancer that allows detection of the extent of the primary as well as abnormal lymph nodes more often than does CT scan. In modern practice,

TABLE 6.1**FIGO STAGING SYSTEM FOR CARCINOMA OF THE VAGINA**

Stage	Description
0	CIS, intraepithelial neoplasia grade 3
I	Limited to the vaginal wall
II	Involvement of the subvaginal tissue but without extension to the pelvic side wall
III	Extension to the pelvic side wall
IV	Extension beyond the true pelvis or involvement of the bladder or rectal mucosa. Bullous edema as such does not permit a case to be allotted to stage IV
IVA	Spread to adjacent organs and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

Source: From Pecorelli S, Beller U, Heintz AP, et al.: FIGO annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat.* 2000; 24:56.

for the majority of patients with disease volume and/or location requiring definitive RT to achieve cure, therapeutic planning will be guided by disease volume assessment utilizing CT, MRI, and/or PET/CT, even though such radiologic modalities are not “allowed” for purposes of staging.

The two commonly used staging systems for carcinoma of the vagina are the FIGO (Table 6.1) and the American Joint Commission on Cancer (TNM) (Table 6.2) classifications. According to FIGO guidelines, patients with tumor involvement of the cervix or vulva should be classified as primary cervical or vulvar cancers, respectively.

PATHOLOGIC CLASSIFICATION

The most common malignant tumor of the vagina is SCC. Melanoma is the second most frequent malignancy. A wide variety of tumors of other types have been described.

Squamous Cell Carcinoma

SCC represents about 80% to 90% of primary vaginal cancers. These tumors occur in older women and are most often located in the upper, posterior wall of the vagina. For a neoplasm to be considered a vaginal primary, there must not be involvement of the cervix or vulva or a history of cervical cancer for 5 years prior to the diagnosis. Histologically,

TABLE 6.2**AMERICAN JOINT COMMISSION ON CANCER (AJCC) STAGING OF VAGINAL CANCER**

PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis/0	CIS
T1/I	Tumor confined to the vagina
T2/II	Tumor invades paravaginal tissues but not to the pelvic wall
T3/III	Tumor extends to the pelvic wall
T4/IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the pelvis (Bullous edema is not sufficient to classify a tumor as T4)
REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1/IVB	Pelvic or inguinal lymph node metastasis
DISTANT METASTASIS (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1/IVB	Distant metastasis
AJCC STAGE GROUPINGS	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T1–3 N1 M0, T3 N0 M0
Stage IVA	T4, any N, M0
Stage IVB	Any T, any N, M1

Source: American Joint Committee on Cancer (AJCC). Vagina. In: Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M eds. *AJCC Cancer Staging Manual*. 6th Ed. New York, NY: Springer-Verlag; 2002:251–257

keratinizing, nonkeratinizing, basaloid, warty, and verrucous variants have been described. Tumors may also be graded as well, moderately, or poorly differentiated, based on a combination of cytologic and histologic features. However, there is little correlation between tumor grade and survival.

Verrucous carcinoma is a rare distinct variant of well-differentiated SCC, usually with the appearance of a large, well-circumscribed, soft, cauliflower-like mass. Verrucous carcinoma may recur locally after surgery, but rarely, if ever, metastasizes.

VAIN is a precursor of SCC and is graded from 1 to 3, based on the thickness of epithelial involvement. Alternatively, VAIN can be classified

as low- or high-grade. High-grade lesions indicate involvement of the outer third of the mucosa, and include CIS, which encompasses the entire thickness of the epithelium. The true incidence of VAIN and its rate of progression to invasive carcinoma are unknown, ranging in several series from 9% to 28%. High-risk HPV was noted in 35% of VAIN 1 and 94% of VAIN 3 lesions. Comparison of the distribution of HPV types in the vagina, vulva, and cervix suggests that VAIN is more closely related to CIN than to VIN.

Clear-Cell Adenocarcinoma and Vaginal Adenosis

DES-associated CCA has a predilection for the upper third of the vagina and the exocervix. It is frequently located at or near the lower margin of the zone of glandular tissue in the vagina or cervix. Most CCAs are exophytic and superficially invasive. About 97% will be associated with mucosal adenosis. CCA is mainly composed of clear and hobnail-shaped cells. The major determinant of outcome in CCA is stage, but some pathologic features are statistically associated with better outcome, including a tubulocystic growth pattern, size less than 3 cm², and less than 3 mm of stromal invasion.

Vaginal adenosis is a condition in which müllerian-type glandular epithelium is present after vaginal development is complete. Although adenosis is the most common histologic abnormality in women exposed to DES in utero, it is not strictly confined to this population. Atypical adenosis of tuboendometrial type appears to be a precursor lesion of CCA.

Other Adenocarcinomas

Primary adenocarcinoma of the vagina is rare and occurs predominantly in postmenopausal women.

Melanoma

Melanoma is the second most common cancer of the vagina, accounting for 2.8% to 5.0% of vaginal neoplasms. The most common locations are the lower third and the anterior vaginal wall. Grossly, these tumors are typically pigmented, and show considerable variation in size, color, and growth patterns, being polypoid or nodular in the majority of cases. Immunohistochemical stains are frequently positive for S100 protein, HMB-45, and melan-A. Tyrosinase and MART-1 are useful markers when S100 is negative or only focally positive. Tumor thickness correlates with prognosis and may be measured by the method of Breslow.

Mesenchymal Tumors

Embryonal RMS is a rare pediatric tumor. The botryoid variant, or sarcoma botryoides, is the most common malignant vaginal tumor in infants

and children. Ninety percent of cases occur in children younger than 5 years of age. Sarcoma botryoides has a characteristic macroscopic appearance consisting of multiple gray-red, translucent, edematous, grape-like masses that fill the vagina and may protrude from it.

Leiomyosarcoma is the most common vaginal sarcoma in adults. Smooth muscle tumors 3 cm or greater in diameter have an increased risk of recurrence. Although they may originate in any part of the vagina, most are submucosal.

PROGNOSTIC FACTORS INFLUENCING CHOICE OF TREATMENT

KEY POINTS

- Primary malignancies of the vagina are all staged clinically.
- The most common malignant tumor of the vagina is squamous cell carcinoma (SCC).
- Vaginal intraepithelial neoplasia is a precursor of SCC.
- Exposure to diethylstilbestrol *in utero* is associated with the development of clear-cell adenocarcinoma.
- Stage of disease is the dominant prognostic factor in terms of outcome.
- Vaginal melanoma has a higher propensity for the development of distant metastases, and these patients do more poorly than patients with SCC.

Invasive Squamous Cell Carcinoma

Stage of disease is the dominant prognostic factor in terms of outcome. In Creasman et al. (1998)'s report, the 5-year survival rate was 96% for patients with stage 0, 73% for stage I, 58% for stage II, and 36% for those with stage III and IV diseases, respectively. In Perez's series, including 165 patients with primary vaginal carcinomas treated with definitive RT, the 10-year actuarial disease-free survival (DFS) was 94% for stage 0, 75% for stage I, 55% for stage IIA, 43% for stage IIB, 32% for stage III, and 0% for those with stage IV.

The impact of lesion location has been controversial. Several investigators have shown better survival and decreased recurrence rates for patients with cancers involving the proximal half of the vagina when compared with those in the distal half or those involving the entire length of the vagina. In addition, lesions of the posterior wall have a worse prognosis than those involving other vaginal walls (10-year recurrence rates of 32% and 19%, respectively), which probably reflect the greater difficulty of performing adequate brachytherapy procedures in this location.

The prognostic importance of lesion size has also been controversial. Chyle et al. (1996) noted that lesions measuring less than 5 cm in maximum

diameter had a 20% 10-year local recurrence rate compared to 40% for those lesions larger than 5 cm. Similarly, in the Princess Margaret Hospital experience, tumors larger than 4 cm in diameter fared significantly worse than smaller lesions. Other data suggest that disease volume, a likely surrogate for stage or lesion size, adversely impacted survival as well as local control.

Several series have shown histologic grade to be an independent, significant predictor of survival. Chyle et al. (1996) also noted histology was a significant predictor of outcome, with a higher incidence of local recurrence in patients with adenocarcinoma compared with SCC (52% and 20%, respectively, at 10 years), as well as a higher incidence of distant metastases (48% and 10%, respectively), and lower 10-year survival rate (20% vs. 50%).

Other Histologies

An increased propensity for distant metastases to the lung and supraclavicular nodes has been reported in patients with CCA. Stage, tubulocystic pattern, size less than 3 cm, and depth of invasion less than 3 mm were all noted to be associated with superior survival.

Vaginal melanoma has a higher propensity for the development of distant metastases, and affected patients do more poorly than patients with SCC.

Patients with malignant mesenchymal tumors of the vagina do less well than those with invasive SCC. Specific, adverse prognostic factors for vaginal sarcoma identified by Tavassoli and Norris included infiltrative versus pushing borders, high mitotic rate of five or more mitoses per ten HPFs, size greater than 3 cm in diameter, and cytologic atypia.

GENERAL MANAGEMENT: TREATMENT OPTIONS AND OUTCOME BY FIGO STAGES

KEY POINTS

- Treatment options for vaginal intraepithelial neoplasia range from partial or complete vaginectomy to more conservative approaches such as local excision, electrocoagulation, laser vaporization, topical 5% fluorouracil, or intracavitary brachytherapy.
- Surgery maybe preferable in select stage I and II patients with SCC lesions at the apex and upper third of the posterior or lateral vagina.
- External beam radiotherapy is advisable in patients with deeply infiltrating or poorly differentiated stage I lesions and in all patients with stage II to IVA disease.
- Consideration should be given to delivering cisplatin-based chemotherapy concurrently with radiotherapy in patients with advanced vaginal cancer.

FIGO Stage 0: Vaginal Intraepithelial Neoplasia—Carcinoma *In-Situ*

VAIN has been approached both surgically and medically by multiple investigators. Treatment options range from partial or complete vaginectomy to more conservative approaches such as local excision, electrocoagulation, laser vaporization, topical 5% fluorouracil (5-FU) administration, or ICB. For patients in whom invasive disease cannot be ruled out, as well as for those who fail conservative therapy, surgical resection remains the treatment of choice. Overall, the reported control rates are very similar among the different approaches, ranging from 48% to 100% for laser, 52% to 100% for colectomy, 75% to 100% for topical 5-FU, and 83% to 100% for RT. The degree of VAIN and the age and general health of the patient are important treatment considerations.

Partial colectomy is favored by many for the treatment of focal VAIN without any prior history of pelvic RT. Patients who have received prior pelvic RT, wherein partial colectomy would have high risk of fistula formation, may benefit from a medical approach with topical application of 5-FU. This acts by inciting a desquamation of the vaginal squamous epithelium, which later reepithelializes with presumably normal cells. Several schedules of topical 5-FU have been reported; however, one preferred schedule is one-third applicator weekly for 10 weeks. It is important that the perineal skin be protected with a topical ointment, such as zinc oxide, to prevent painful vulvar erosions regardless of which 5-FU application schedule is chosen. More recently, investigators have demonstrated the feasibility and likely efficacy of imiquimod in the treatment of VAIN.

Partial or total vaginectomy has been considered by many to be an acceptable treatment for VAIN. However, one of its main drawbacks is shortening or stenosis of the vagina, frequently with poor functional results. Prior RT is probably a contraindication to vaginectomy owing to significantly increased morbidity. Control rates of 66% to 100% following partial colectomy have been achieved.

RT has a long history of documented efficacy with control rates ranging between 80% and 100%, and a significantly better therapeutic ratio than other modalities. Using conventional low dose-rate (LDR) ICB techniques, the entire vaginal mucosa should receive between 50 and 60 Gy, given the high incidence of multicentricity; the area of involvement should receive 70 to 80 Gy, in one or two implants, prescribed to the mucosal surface. Higher doses may cause significant vaginal fibrosis and stenosis. Perez et al. (1999) reported only one distal local failure in the 20 patients treated for CIS. Pelvic recurrences or distant failures have not been observed in the absence of invasive component, after ICB.

There have been some reports in the literature regarding the use of high dose-rate (HDR) ICB for patients with VAIN III; however, data are limited. Based on the excellent local control and functional results obtained with LDR-ICB, this remains the treatment of choice when definitive RT is used.

Invasive Squamous Cell Carcinoma

Surgical Approach and Outcomes

In general, SCC of the vagina has been treated with RT. However, several surgical series have reported acceptable to excellent outcomes in well-selected patients, with survival rates after radical surgery for stage I disease ranging from 75% to 100%. Cases in which surgery may be the preferred treatment include selected stage I and II patients, with lesions at the apex and upper third of the posterior or lateral vagina that could be approached with radical hysterectomy, upper vaginectomy, and pelvic lymphadenectomy providing adequate margins for very superficial lesions. Lesions in the lower third of the vagina would require vulvovaginectomy in addition to dissection of inguinofemoral nodes to achieve negative margins. If the margins are found to be close or positive after resection, adjuvant RT is recommended. However, for lesions at other sites, and those cases requiring more extensive resection, definitive RT is the treatment of choice since it offers excellent results. Exenteration should be reserved for those with central failure after RT, or as primary therapy in those with disease not fixed to the bone.

Advanced-stage patients should receive definitive RT, probably in combination with concurrent chemotherapy, although the role of combined modality therapy is unknown.

Radiation Therapy Techniques and Outcome

Stage I

In patients with stage I lesions, usually 0.5 to 1 cm thick that may involve one or more vaginal walls, it is important to individualize radiation therapy techniques to obtain optimal functional results. Superficial lesions can be adequately treated with ICB alone using afterloading vaginal cylinders. The entire length of the vagina is generally treated to a mucosal dose of 60 to 65 Gy (LDR), and an additional mucosal dose of 20 to 30 Gy is delivered to the area of tumor involvement. For lesions thicker than 0.5 cm at the time of implantation, it is advisable to combine ICB and interstitial brachytherapy (ITB) with a single-plane implant to increase the depth dose and limit excessive irradiation to the vaginal mucosa. An additional 15 to 20 Gy at a depth of 0.5 cm beyond the plane of the implant will be delivered with the ITB such that the base of the tumor receives between 65 and 70 Gy, with the involved vaginal mucosa receiving an estimated 80 to 100 Gy. The proximal and distal vaginal mucosal doses should be limited to 140 and 100 Gy, respectively.

There is general consensus that external beam radiotherapy (EBRT) is advisable for larger, more infiltrating or poorly-differentiated tumors that may have a higher risk of lymph node metastasis. The whole pelvis is treated with 10 to 20 Gy; an additional parametrial dose should be delivered with a midline block (5 half-value layer [HVL]) to give a total of 45 to 50 Gy to the parametria and pelvic side walls. Chyle et al. (1996) recommended EBRT in addition to brachytherapy for stage I disease to cover at least the paravaginal nodes, and, in larger lesions, to cover the external and internal iliac nodes.

About 95% to 100% of local control has been achieved with intracavitary and interstitial techniques, with 5-year survival for patients with stage I disease treated with RT alone ranging from 70% to 95% (Table 6.3).

Stage II

Patients with stage IIA tumors have more advanced paravaginal disease without extensive parametrial infiltration. These patients are uniformly treated with EBRT followed either by ICB and/or ITB. Generally, the whole pelvis receives 20 Gy followed by an additional parametrial dose with a midline 2- to 4-cm-wide (5 HVL) block, depending on the width of the implant, to deliver a total of 45 to 50 Gy to the pelvic side walls. A combination of LDR-ICB or LDR-ITB may be used to deliver a minimum of 50 to 60 Gy 0.5 cm beyond the deep margin of the tumor (in addition to the

TABLE 6.3

FIGO STAGE I AND II VAGINAL CANCERS: TREATMENT APPROACH AND RESULTS

Treatment Modality Author	No. of Patients	Outcome—Survival
Irradiation ± surgery		
Chyle	59 St I	10 year 76%
	104 St II	10 year 69%
Creasman (NCDB)	169 St I	5-year surv. 73%; 79% S + RT (47), 63% RT (122)
	175 St II	5-year surv. 58%; 58% S + RT (39), 57% RT (136)
Davis	19 St I	5-year surv. 100% S + RT (5), 65% RT (14)
	18 St II	5-year surv. 69% S + RT (9), 50% RT (9)
Kirkbride	40 St I	5 year 72%
	38 St II	5 year 70%
Kucera	16 St I	5 year 81%
	23 St II	5 year 43.5%
Perez	59 St I	10 year 80%
	63 St IIA	10 year 55%
	34 St IIB	10 year 35%

(continued)

TABLE 6.3

FIGO STAGE I AND II VAGINAL CANCERS: TREATMENT APPROACH AND RESULTS (*continued*)

Treatment Modality Author	No. of Patients	Outcome–Survival
Stock	8 St I	5 year 100% S + RT, 80% RT
	35 St II	5 year 69% S + RT, 31% RT
Urbanski	33 St I	5 year 73%
	37 St II	5 year 54%
Frank	50 St I	5-year DSS, 85%
	97 St II	5-year DSS, 78%
Radical surgery		5-year surv.
Ball	19 St I	84%
	8 St II	63%
Creasman (NCDB)	76 St I	90%
	34 St II	70%
Davis	25 St I	85%
	27 St II	49%
Rubin	5 St I	80%
	3 St II	33%
Stock	17 St I	56%
	23 St II	68%
Tjalma	26 ^a	91%

^aFour patients received adjuvant irradiation.

St, stage; RT, radiotherapy; S, surgery; surv., survival; DSS, disease specific survival.

Source: Adapted from Cardenes VR, Schilder JM, Roth LM. Chapter 21: Vagina.

In: *Principles and Practices of Gynecologic Oncology*, 5th Ed. Baltimore, MD: Lippincott Williams & Wilkins; 2009:602.

whole pelvis dose, to a total tumor dose of 70 to 80 Gy). Double-plane or volume implants may be necessary for more extensive disease. Perez et al. (1999) showed that in stage IIA, the local tumor control was 70% (37 of 53) in patients receiving brachytherapy combined with EBRT, compared with 40% (four of ten) in patients treated with either brachytherapy or EBRT alone. The superiority of the combination of EBRT and brachytherapy over EBRT or brachytherapy alone has been as well shown in other series.

Patients with stage IIB, with more extensive parametrial infiltration, will receive 40 to 50 Gy, whole pelvis and 55 to 60-Gy total parametrial

dose (with midline shielding). An additional boost of 30 to 35 Gy will be given with LDR interstitial and ICB, to deliver a total tumor dose of 75 to 80 Gy to the vaginal tumor and 65 Gy to parametrial and paravaginal extensions. The pelvic side wall dose should be kept below 60 Gy (including the contributions of EBRT and brachytherapy). Patients with lesions limited to the upper third of the vagina can be treated with an intrauterine tandem and vaginal ovoids or cylinders. The local-regional control in patients with stage IIB in Perez's series was also superior with combined EBRT and brachytherapy (61% vs. 50%, respectively).

The 5-year survival for patients with stage II disease treated with RT alone ranges between 35% and 70% for stage IIA, and 35% and 60% for stage IIB. The results of several series published in the literature using different treatment approaches for stage I and II vaginal cancers are shown in Table 6.3.

Stages III and IVA

Generally, patients with stage III and IVA diseases will receive 45 to 50 Gy EBRT to the pelvis, and in some cases, additional parametrial dose with midline shielding to deliver up to 60 Gy to the pelvic side walls. Ideally, ITB brachytherapy boost is performed, if technically feasible, to deliver a minimum tumor dose of 75 to 80 Gy. If brachytherapy is not feasible, a shrinking-field technique can be used, with fields defined using the three-dimensional treatment planning capabilities to deliver a tumor dose around 65 to 70 Gy. An alternative approach is intensity-modulated RT (IMRT) using multiple beams of varying intensity that conform the high-dose region to the shape of the target tissues, with more adequate sparing of the surrounding normal tissues, primarily the bladder, rectum, and small bowel.

The overall cure rate for patients with stage III disease is 30% to 50%. Stage IVA includes patients with rectal or bladder mucosa involvement, or in most series, positive inguinal nodes. Although some patients with stage IVA disease are curable, many patients are treated palliatively with EBRT only. Pelvic exenteration can also be curative in highly selected stage IV patients with small-volume central disease. Table 6.4 shows the treatment results with different therapeutic modalities, including four series that reported the use of primary surgery in highly selected patients with advanced disease. However, each of these series reported a far greater number of patients with similar stage disease treated with RT, which represents the preferred approach in contemporary practice.

External Beam Radiotherapy

EBRT is advisable in patients with deeply infiltrating or poorly-differentiated stage I lesions and in all patients with stage II to IVA diseases. The treatment is generally delivered using opposed anterior and posterior fields (AP/PA). The pelvis receives between 20 and 45 Gy depending on the stage of the disease. This will be followed, in some cases, by bilateral pelvic side wall boosts to 50 to 55 Gy. High-energy photons (≥ 10 MV) are usually preferred. CT simulation is highly encouraged since it allows

TABLE 6.4**FIGO STAGE III AND IV VAGINAL CANCERS: OUTCOME WITH RADIATION THERAPY WITH/WITHOUT SURGERY**

Treatment Modality Author	No. of Patients	Outcome–Survival
Irradiation ± surgery		
Chyle	55 St III	10 year 47%
	16 St IV	10 year 27%
Creasman (NCDB)	St III and IV, 180	5-year surv. 36%; 60% S + RT (36), 35% RT (144)
Kirkbride	42 ^a St III and IV	5 year 53%
Kucera	46 St III	5 year 35%
	19 St IVA	5 year 32%
Perez	20 St III	10 year 38%
	15 St IV	0%
Stock	9 St III	5 y 0%
	8 St IV	0%
Urbanski	40 St III	5 year 22.5%
	15 St IVA	0%
Frank	46 St III and IVA	5-year DSS, 58%
Radical surgery		5-year surv.
Ball	2 St III	50%
Creasman (NCDB)	St III and IV, 21	47%
Rubin	2 St III	50%

^aTwenty patients with stages III and IV were treated with chemotherapy (5-FU ± mitomycin-C) and radiotherapy.

St, stage; RT, radiotherapy; S, surgery; surv., survival; DSS, disease specific survival.

a more accurate delineation of the regional lymph node areas. Treatment portals cover at least the true pelvis with 1.5- to 2.0-cm margin beyond the pelvic rim. Superiorly, the field extends to either L4–5 or L5–S1 to cover the pelvic lymph nodes up to the common iliacs, and extends distally to the introitus to include the entire vagina. Lateral fields, if used, should extend anteriorly to adequately include the external iliac nodes, anterior to the pubic symphysis, and at least to the junction of S2–3 posteriorly.

In patients with tumors involving the middle and lower vagina with clinically negative groins, the bilateral inguino-femoral lymph node regions should be treated electively to 45 to 50 Gy. Planning CT is recommended to determine adequately the depth of the inguino-femoral nodes. A number of techniques have been used to treat the areas at risk without overtreating the femoral necks. Some of the most commonly used techniques include the use of unequal loading (2:1, AP/PA), a combination of low- and high-energy photons (4 to 6 MV, AP, and 15 to 18 MV, PA), or equally weighted beams with a transmission block in the central AP field, utilizing small AP photon or electron beams to deliver a daily boost to the inguino-femoral nodes.

For patients with positive pelvic nodes or those patients with advanced disease not amenable to interstitial implant, additional boost to the areas of gross disease, as defined by CT scan, should be given using conformal therapy to deliver a total dose between 65 and 70 Gy, when feasible, with high-energy photons. Boost to the areas of gross nodal disease, as defined by CT scan, should be given using small fields (similar to the parametrial boost with midline shielding) to deliver a total dose between 60 and 65 Gy with high-energy photons. In patients with clinically palpable inguinal nodes, additional doses of 15 to 20 Gy (calculated at a depth determined by CT scan) are necessary with reduced portals. This is generally achieved by using low-energy photons or electron beam (12 to 18 MeV). IMRT techniques are now available to deliver higher doses to the gross disease while reducing the dose to the bladder and rectum.

Overall treatment time (7 to 9 weeks) has been found to be a significant treatment factor predicting tumor control, although this has not been universally recognized.

Low Dose–Rate Intracavitary Brachytherapy

VAIN and small T1 lesions with less than a 0.5-cm depth can be adequately treated with ICB alone. LDR-ICB is performed using vaginal cylinders loaded with cesium-137 (^{137}Cs) radioactive sources. Ninety-five percent of vaginal lymphatic channels are located within a 3-mm depth from the vaginal surface, confirming the adequacy of prescribing the dose to a depth of 5 mm for superficially invasive lesions.

It is recommended that the largest possible diameter that can be comfortably accommodated by the patient should be used to improve the ratio of mucosa to tumor dose, and eliminate vaginal rugations. In general, the vulva is sutured closed for the duration of the implant in order to secure the position of the applicators.

In patients with upper vagina lesions with less than a 0.5-cm depth of invasion, vaginal colpostats alone (after hysterectomy) or in combination with intrauterine tandem, loaded with ^{137}Cs sources similar to that used in treatment of cervical cancer, can be used to treat the proximal vagina to a minimum dose of 65 to 70 Gy, estimated to 0.5-cm depth, including the contribution of EBRT if given. When indicated, the remainder of the vagina can be treated by performing a subsequent implant using vaginal cylinders (generally 50 to 60 Gy prescribed to the vaginal surface).

High Dose–Rate Intracavitary Brachytherapy

The International Commission of Radiation Units (ICRU) defines HDR brachytherapy as exceeding 12 Gy/hour. HDR-ICB is typically performed with a 10 Ci single Iridium-192 (^{192}Ir) source (Micro-Selectron HDR, Nucletron). The applicators are similar to those described for LDR. Generally, the number of insertions ranges from one to six (median, three), with the dose per fraction ranging from 300 to 800 cGy (median, 700 cGy). Complications analyses from retrospective data show no significant differences between the HDR and the LDR.

Interstitial Brachytherapy

ITB is an important component in the treatment of more advanced primary vaginal carcinomas, typically in combination with EBRT and/or ICB. As a general rule, temporary implants are more commonly used in the curative treatment of larger gynecologic malignancies, whereas permanent implants are usually performed for smaller volume disease. When performing an interstitial procedure, freehand implants or template systems designed to assist in preplanning and to guide and secure the position of the needles in the target volume can be employed. These templates generally consist of a perineal template, vaginal obturator, and 17-gauge hollow guides of various lengths that can be afterloaded with ^{192}Ir sources. The vaginal obturator is centrally drilled so that it can allow the placement of a tandem to be loaded with ^{137}Cs sources. This makes it possible to combine an interstitial and intracavitary application simultaneously. The major advantage of these systems is greater control of the placement of the sources relative to tumor volume and critical structures owing to the fixed geometry provided by the template. In order to improve the accuracy of target localization and needle placement as well as improve avoidance of normal structures, several investigators have explored performing ITB under transrectal ultrasound, CT, MRI-planned implants with endorectal coil, laparotomy, and laparoscopic guidance.

Tewari and associates described results in 71 patients who underwent ITB with (61 patients) or without (10 patients) EBRT. Each implant delivered a total tumor dose reaching 80 Gy integrated with EBRT. Local control was achieved in 53 patients (75%). By stage, 5-year DFS rates included stage I, 100%; stage IIA, 60%; stage IIB, 61%; stage III, 30%; and stage IV, 0%. Significant complications occurred in nine patients (13%) including necrosis ($n = 4$), fistulas ($n = 4$), and small bowel obstruction ($n = 1$).

Role of Chemotherapy and Radiation

The control rate in the pelvis for stage III and IV patients is relatively low, and about 70% to 80% of the patients have persistent disease or recurrent disease in the pelvis in spite of high doses of EBRT and brachytherapy. Failure in distant sites does occur in about 25% to 30% of the patients with locally advanced tumors, which is much less than pelvic recurrences. Therefore, there is a need for better approaches to the management of advanced disease such as the use of concomitant chemoradiotherapy. Agents such as 5-FU, mitomycin, and cisplatin have shown promise when combined with

RT, with complete response rates as high as 60% to 85%, but long-term results of such therapy have been variable, in part owing to the advanced stage of the patients included in these small studies. Extrapolating from recently published data on locally advanced cervical cancer demonstrating an advantage in locoregional control, overall survival, and DFS for patients receiving cisplatin-based chemotherapy concurrently with RT as well as data on loco-regionally advanced vulvar cancer, consideration should be given to a similar approach in patients with advanced vaginal cancer.

PATTERNS OF FAILURE IN SQUAMOUS CELL CARCINOMA

At least 85% of patients who recur will have a component of locoregional failure, and the vast majority of these recurrences will be confined to the pelvis and vagina. The rate of locoregional recurrence in stage I is approximately 10% to 20% versus 30% to 40% in stage II. The pelvic control rate for patients with stage III and stage IV is relatively low and about 50% to 70% of the patients have recurrences or persistence in spite of well-designed RT. The median time to recurrence is 6 to 12 months. Tumor recurrence is associated with a dismal prognosis, with only a few long-term survivors after salvage therapy. Failure in distant sites alone or associated with locoregional failure does occur in about 25% to 40% of patients with locally advanced tumors.

TREATMENT COMPLICATIONS

KEY POINTS

- At least 85% of patients who recur will have a component of locoregional failure, with the vast majority of these recurrences being confined to the pelvis and vagina.
- The median time to recurrence is 6 to 12 months.
- Tumor recurrence is associated with a dismal prognosis.
- Acute radiation toxicity usually resolves within 2 to 3 months after completion of therapy.

The anatomic location of the vagina places the lower gastrointestinal and genitourinary tracts at greatest risk for complications after surgery or RT.

Acute toxicity from vaginal irradiation includes edema, erythema, moist desquamation, and confluent mucositis with or without ulceration, and the severity of the acute effects varies in intensity and duration depending upon patient age, hormonal status, tumor size, stage, RT dose, and personal hygiene. These effects usually resolve within 2 to 3 months after the completion of therapy. Chemotherapy concurrently with RT enhances the acute mucosal response to both EBRT and brachytherapy.

The effects of chemotherapy on the incidence of late complications, if any, are unclear.

Late effects include the development of vaginal atrophy, fibrosis, and stenosis. Telangiectasis is commonly seen in the vagina. Vaginal narrowing or shortening, paravaginal fibrosis, loss of elasticity, and reduced lubrication often result in dyspareunia. More severe complications include necrosis with ulceration that can progress to fistula formation (rectovaginal, vesicovaginal, and urethrovaginal). Most series report major complication rates ($>Gr\ 2$) of 16% to 17% at 10 years.

The RT tolerance limit of the surface of the proximal vagina is 140 Gy. The distal vaginal tolerance is lower and should be limited to surface doses of less than 90 Gy. In addition, the posterior wall of the vagina is more prone to radiation injury than the anterior and lateral walls, and the dose should be kept below 80 Gy in order to minimize the risk of rectovaginal fistula.

CLEAR CELL CARCINOMA OF THE VAGINA

Stage I CCA of the vagina is adequately managed with surgery, with one series of 142 cases noting an 8% risk of recurrence after radical surgery ($n = 117$), and an 87% survival. As the majority of CCAs occur in the upper third of the vault, the largest series addressing the surgical approach to these lesions have advocated radical hysterectomy, pelvic and paraaortic lymphadenectomy, and sufficient colpectomy to achieve negative margins. Wharton et al. advocate intracavitary or transvaginal irradiation for the treatment of small tumors because this may yield excellent tumor control with a functional vagina and preservation of ovarian function. A combination of wide local excision and extraperitoneal node dissection followed by brachytherapy is an acceptable alternative for patients desirous of fertility preservation.

Most patients with stage II vaginal CCA should be treated with combination EBRT and brachytherapy; however, small, easily resectable lesions in the upper fornix might undergo resection, allowing better preservation of coital and ovarian function.

NONEPITHELIAL TUMORS OF THE VAGINA

KEY POINT

- As distant disease is the predominant pattern of failure in patients with vaginal melanoma, quality of life should be optimized by offering management with wide excision followed by RT and avoiding disfiguring radical surgery.

Melanoma of the Vagina

Vaginal melanoma is an exceedingly rare entity, and with its propensity to develop distant metastases and its lack of a recognized precursor lesion, it

has presented therapeutic challenges with generally disappointing results irrespective of treatment modality. Because vaginal melanoma was deemed a relatively radioresistant tumor, radical surgery had been the treatment of choice in operable patients. However, most series report 5-year survival rates of 5% to 30% regardless of radicality of surgery. As distant disease is the predominant pattern of failure in these patients, quality of life should be optimized by wide excision followed by RT to affect local control, while obviating the need for disfiguring radical surgery.

Recent retrospective data also suggest that vaginal melanoma is reasonably radioresponsive and possibly radiocurable. Volumes and doses of irradiation are similar to those used for epithelial tumors, ranging from 50 Gy for subclinical disease to 75 Gy for gross tumors. Several series have now shown that prolonged local control can be obtained with RT as an adjunct to more limited surgery, or even with RT alone, primarily in patients with lesions ≤ 3 cm in diameter. The use of systemic chemotherapy and/or immunotherapy has been very disappointing in the limited published data.

Sarcomas of the Vagina

Sarcomas represent 3% of vaginal primaries with leiomyosarcoma representing 50% to 65% of vaginal sarcomas, with the majority arising from the posterior vaginal wall. Histopathologic grade appears to be the most important predictor of outcome. Radical surgical resection, such as posterior pelvic exenteration, offers the best chance for cure for vaginal leiomyosarcomas. Sarcomas are relatively resistant to chemotherapy, and the most common site of failure is the pelvis. In 50% of patients with recurrence, it is the only site of failure. Five-year survival rates are generally better in patients with leiomyosarcoma than in patients with MMMT. Adjuvant RT seems to be indicated in patients with high-grade tumors and locally recurrent low-grade sarcomas.

Embryonal RMS of the vagina, the most common pediatric vaginal tumor, is appropriately managed through the use of multimodality therapy. A series of reports from the Intergroup Rhabdomyosarcoma Study Group (IRSG) have reported survival rates in excess of 85% utilizing VAC chemotherapy and wide excision with or without adjuvant RT, sparing the great majority of patients from exenterative surgery.

SALVAGE THERAPY

This group represents a heterogeneous population, and careful workup to establish the extent of disease is crucial. Local recurrences should be confirmed by biopsy. In most cases, only patients with small volume local recurrences and no metastatic disease are curable.

Generally, patients with isolated pelvic or regional recurrences after definitive surgery who have not received prior RT are managed with EBRT, often in conjunction with brachytherapy. Concurrent cisplatin-based chemotherapy may also be recommended, and extrapolation from the available data for locally advanced cervical and vulvar cancer suggests that

a combined modality approach with chemoradiation may improve the locoregional control and survival in patients with isolated pelvic recurrences. Salvage options for patients with central recurrence after definitive or adjuvant RT are limited to radical surgery, usually exenterative, or, in selected patients with small volume disease, reirradiation using interstitial radiation implants or highly conformal three-dimensional EBRT. In patients with small, well-defined vulvovaginal or pelvic recurrences, reirradiation using primarily interstitial techniques has been attempted with control rates between 50% and 75% and grade 3 or higher complication rates between 7% and 15%.

PALLIATIVE THERAPY

Radiation Therapy

At the present time, there is no curative option for patients who present with stage IVB disease. Many of these patients suffer from severe pelvic pain or bleeding. Palliative radiation with either ICB (for vaginal bleeding) or EBRT can result in good tumor regression and excellent palliation of symptoms.

Chemotherapy in Advanced and Recurrent Vaginal Cancer

Treatment of recurrent or metastatic disease is confined to a handful of phase II clinical trials and anecdotal reports. In general, regimens that are active in cervical cancer are usually active in vaginal cancer. Regimens including cisplatin, mitoxantrone, 5-FU, mitomycin C, bleomycin, vincristine, and MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) have been reported with varying success.

Suggested Readings

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CHAPTER 7 ■ THE UTERINE CERVIX

EPIDEMIOLOGY

Worldwide, cervical cancer is the second most common cancer (after breast cancer) in women, and is the leading cause of death of women from cancer in developing countries. Nearly one-half million new cases occur each year with the majority of cases occurring in developing countries lacking access to routine Papanicolaou (Pap) smear screening. Cervical carcinoma is the twelfth most common malignant tumor in women in the United States, and while the incidence and mortality of this disease in North America have declined during the last half-century, black and Hispanic women continue to be disproportionately affected.

RISK FACTORS AND ETIOLOGY

KEY POINTS

- Cervical cancer is a sexually transmitted disease associated with chronic infection by oncogenic types of human papillomavirus (HPV).
- Tobacco smoking may be a cofactor for the development of high-grade cervical dysplasia in women who have chronic HPV infections.
- HPV 16 and 18 account for approximately 70% of cervix cancers.

Cervical cancer is a sexually transmitted disease associated with chronic infection by oncogenic types of human papillomavirus (HPV). Therefore, risk factors for cervical cancer are the same as those for sexually transmitted disease, including early age at onset of sexual activity, multiple pregnancies, long duration of oral contraceptive use, other sexually transmitted infections including chlamydia and herpes simplex virus, immunosuppressed states such as renal transplant, and multiple sexual partners. Tobacco smoking is also a risk factor for cervical cancer and may be a cofactor for development of high-grade cervical dysplasia in women who have chronic HPV infections.

Human Papillomavirus

HPV is a double-stranded DNA virus, with more than 30 recognized oncogenic and more than 70 non-oncogenic strains of HPV being described to date.

In the United States, HPV 16 and 18 account for approximately 70% of cervix cancers. High-risk HPV genotypes code for three early proteins (E5, E6, and E7) with cellular growth-stimulating and transforming properties. The E6 protein binds to p53, results in chromosomal instability, activates telomerase, inhibits apoptosis, and results in cellular immortalization. The E7 protein binds to retinoblastoma protein (Rb), inactivating the Rb-related pocket proteins, activates cyclins E and A, inhibits cyclin-dependent kinase inhibitors, and also results in cellular immortalization. HPV E6 and E7 lead to dysplasia and malignant transformation of cervical epithelium. High-risk HPV types are identified in a high percentage of patients with adenocarcinoma of the cervix and small cell carcinoma of the cervix in addition to the more common squamous carcinoma of the cervix.

Cellular and humoral immune responses are likely to be involved in the resolution of HPV infection, and deficiencies, such as caused by human immunodeficiency virus (HIV) infection, may result in more rapid progression to dysplasia and carcinoma.

Almost 50% of women will be infected with the HPV within 4 years after the onset of sexual activity, with prevalence peaking between 25 to 35 years of age. Despite a high prevalence of HPV, only 5% to 15% will develop cervical dysplasia.

Concurrent Infection with HPV and Human Immunodeficiency Virus

HIV is a sexually transmitted virus that results in a decline in circulating CD4+ cells over time. Concurrent infection with HIV and HPV may result in more rapid progression from chronic HPV infection to dysplasia and cancer, and HIV+ patients with concurrent HPV infection must be followed closely and aggressively treated for squamous intraepithelial lesions. Antiretroviral therapy does not affect HPV-related disease in HIV-infected patients.

ANATOMY

The cervix is an extension of the lower uterine segment of the uterus. The cervix varies in length, averaging 3 to 4 cm. Centrally in the vaginal portion is the external cervical os, which connects to the endocervical canal, the internal cervical os, and the endometrial canal.

The cervix is lined by squamous and columnar cells. The transition from columnar cells to squamous cells occurs in the region of the cervical os known as the transformation zone. Most cervical dysplasias and invasive cancers arise from this area. The endocervix contains mostly mucinous glandular epithelium.

The uterus has five ligamentous attachments. Specifically these include the round, broad, utero-ovarian, cardinal, and uterosacral ligaments. Within the leaves of the broad ligament are extraperitoneal connective tissues, known as the parametrium. The blood supply of the uterus is mainly

through the uterine artery, originating from the anterior division of the hypogastric artery. The lymphatics of the cervix drain into the paracervical and parametrial lymph nodes and to the internal, external, and common iliac chains. The obturator lymph nodes are the most medial portion of the external iliac nodal region. Other lymphatic drainage routes include the inferior and superior gluteal lymph nodes and the superior rectal, presacral, and paraaortic lymph nodes. The innervations of the cervix are from the sacral roots (S2–4).

NATURAL HISTORY

KEY POINTS

- An interval of epithelial dysplastic changes, typically in the transformation zone, known as cervical intraepithelial neoplasia, precedes the development of invasive cancer.
- The reported rate of progression of carcinoma *in situ* to invasive cancer ranges from 12% to 22%.
- The pattern of lymphatic metastases is predictable and orderly as the rate of paraaortic lymph node metastasis is very rare if the pelvic nodes are uninvolved.
- The most common sites of hematogenous spread include lung, mediastinum, bone, and liver.
- Most recurrences occur in the first 24 months with a median of 17 months.

Preinvasive Disease

Cervical cancer is preceded by an interval of epithelial dysplastic changes, typically in the transformation zone, known as cervical intraepithelial neoplasia (CIN), which may progress to invasive cancer. Low-grade dysplasia (CIN 1) is confined to the basal one third of the epithelium, and most low-grade lesions will regress to normal in about 24 months. Full thickness involvement is known as CIN 3 or carcinoma *in situ* (CIS). Overall, the reported rate of progression of CIS to invasive cancer ranges from 12% to 22%.

Patterns of Spread

Cervical cancer can spread through direct extension to the endocervix, lower uterine segment, parametrium, vagina, and, less often, to the bladder and/or rectum. It can also spread through the lymphatics to the parametrial, obturator, and internal, external, and common iliac lymph nodes. The pattern of spread is usually predictable and orderly as the rate of paraaortic lymph node metastasis is very rare if the pelvic nodes were spared. The overall risk of pelvic lymph node metastasis in stage IB is about 17%.

The risk of paraaortic nodal metastasis is higher with advanced stage, with rates of 16% and 25% for stages II and III, respectively. The most common sites of hematogenous spread include lung, mediastinum, bone, and liver. Most recurrences occur in the first 24 months with a median of 17 months.

CLINICAL PRESENTATION AND DIAGNOSTIC EVALUATION

KEY POINTS

- The two primary means of obtaining and diagnosing cervical dysplasia are the conventional Papanicolaou smear and liquid-based thin layer preparation.
- The combination of negative cytology and human papillomavirus (HPV) testing carries a high negative predictive value of over 95% regarding the development of cervical intraepithelial neoplasia (CIN) 3 or invasive cancer.
- HPV testing is more sensitive in detecting high-grade disease compared to conventional smears but it has a lower specificity rate.
- Indications for colposcopy include an abnormal appearing cervix, persistent postcoital bleeding or discharge, persistent CIN 1, 2, or 3 on cytology, *in utero* exposure to diethylstilbestrol (DES), and atypical squamous cells of uncertain significance (ASCUS) smears with positive high-risk HPV testing.

Preclinical Invasive Disease

Screening and Cytology

The two primary means of obtaining and diagnosing cervical dysplasia are the conventional Pap smear and the liquid-based thin layer preparation. Although the data are conflicting, it appears that liquid-based cytology may be superior to conventional cytology, increasing detection rates of low- and high-grade abnormalities. The current recommendation is to start cytologic screening within 3 years after the onset of sexual activity or when a woman reaches the age of 21. The American Cancer Society (ACS) recommends annual screening until age 30 with conventional Pap smear or every other year if liquid-based cytology is used. If a woman has two to three normal smears, the screening interval can be lengthened to every 2 to 3 years. High-risk women should be screened annually. ACS recommends stopping at age 70 if there have been three consecutive negative smears in the past 10 years.

HPV Testing

The combination of negative cytology and HPV testing carries a high negative predictive value of over 95% regarding the development of CIN 3

or invasive cancer, providing great reassurance for low-risk women and lengthening the interval of screening in that population to 3 years.

HPV testing is much more sensitive in detecting high-grade disease compared to conventional smears but with a lower specificity rate. Screening women younger than 30 may lead to unnecessary testing as many HPV infections are transient, and most women will not develop dysplasia with HPV infection. In low-grade squamous intraepithelial lesion, more than 85% of cases test positive for HPV. Therefore, HPV testing is not encouraged. HPV testing appears to be useful in triage of ASCUS smears, possibly reducing colposcopic referrals by almost 50%.

Colposcopy

Colposcopy examines the lower genital tract including the vulva, vagina, and epithelium of the cervix and opening of the endocervix. The use of acetic acid and Lugol solution assists in highlighting abnormal changes that could signify high-grade disease such as aceto-white plaques and vascular abnormalities (punctations, mosaicism, and abnormal branching). Indications for colposcopy include an abnormal appearing cervix; persistent postcoital bleeding or discharge; persistent CIN 1, 2, or 3 on cytology; *in utero* exposure to diethylstilbestrol; and ASCUS smears with positive high-risk HPV testing. Adequate colposcopic examination mandates full visualization of the entire transformation zone and endocervical curettage (ECC).

Conization Biopsy

Cervical conization refers to the surgical removal of the squamo-columnar junction. This may be done in the operating suite through a classical cold knife conization technique or as an outpatient using thermal cautery with loop excision. Indications for conization include inadequate colposcopy; positive ECC; persistent CIN 1 (usually >1 year); CIN 2, 3; or CIS; and discrepancy between cytologic, colposcopic, or pathologic findings.

Clinical Disease

Symptoms and Complaints

The most common presentations of invasive cervical cancer are abnormal vaginal bleeding, postcoital bleeding, and vaginal discharge. As the tumor enlarges, it can cause local symptoms such as pelvic pain and difficulty with urination or defecation. As the disease metastasizes to regional lymph nodes, back pain, leg swelling (especially unilateral), and neuropathic pain may occur.

Physical Findings

The most common finding on physical examination is an abnormal lesion on the cervix, at times necrotic and friable. Possible extension onto the

vaginal wall should be assessed. Determination of parametrial, sidewall, and uterosacral ligament involvement must be done through a rectovaginal examination. Other areas of concern are the superficial groin and femoral lymph nodes and the supraclavicular region.

Staging

KEY POINTS

- Cervical cancer is clinically staged by physical examination and limited radiographic evaluation.
- Positron emission tomography has emerged as a superior method of imaging nodal disease in cervical cancer.
- Surgical findings and radiographically guided biopsies of suspected lesions cannot be used to change or modify clinical FIGO staging.
- The diagnosis of microinvasive disease must be made on a conization or hysterectomy specimen.

Laboratory Studies

A complete peripheral blood count is indicated to evaluate for anemia, which might warrant correction. Serum chemistries with attention to serum creatinine are essential to evaluate for renal failure or assess renal function in patients who will receive cisplatin-based chemoradiotherapy. Additional tests should include liver functions and urinalysis.

Radiographic Studies

Cervical cancer is clinically staged by physical examination and limited radiographic evaluation. Computed tomography (CT) and magnetic resonance imaging (MRI) are used extensively to delineate disease extent and improve treatment planning but do not change the assigned staging. Several studies and a meta-analysis have shown an increased sensitivity for MRI as compared with CT for the evaluation of tumor size, uterine body involvement, and extent of disease.

Modern imaging techniques, such as CT and MRI, have low sensitivities for detecting disease in the paraaortic nodes less than 1 cm. Positron emission tomography (PET) has emerged as a superior method of imaging nodal disease in cervical cancer. The reported sensitivity is about 84%.

FIGO and American Joint Committee Commission on Cancer Staging

The staging system used for cervical cancer is based on the 2009 Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) staging system and is shown in Table 7.1. Stage IA1 is defined as stromal invasion

TABLE 7.1**FIGO STAGING OF CARCINOMA OF THE UTERINE CERVIX
(UPDATED 2009)**

Stage I: The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).

IA: Invasive carcinoma that can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≤ 7 mm.

IA1: Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm.

IA2: Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not more than 7.0 mm.

IB: Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA.*

IB1: Clinically visible lesion ≤ 4.0 cm in greatest dimension.

IB2: Clinically visible lesion > 4.0 cm in greatest dimension.

Stage II: Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.

IIA: Without parametrial invasion.

IIA1: Clinically visible lesion ≤ 4.0 cm in greatest dimension.

IIA2: Clinically visible lesion > 4 cm in greatest dimension.

IIB: With obvious parametrial invasion.

Stage III: The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney.**

IIIA: Tumor involves lower third of the vagina, with no extension to the pelvic wall.

IIIB: Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.

Stage IV: The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.

IVA: Spread of the growth to adjacent organs.

IVB: Spread to distant organs.

*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of no > 7.00 mm. Depth of invasion should not be > 5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with “early (minimal) stromal invasion” (~ 1 mm).

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Source: From Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009;105:103–104.

to less than or equal to 3 mm in depth and no wider than 7 mm; stage IA2 is defined as stromal invasion of 3 to 5 mm with width of no greater than 7 mm. In addition to size criteria, the Society of Gynecologic Oncologists (SGO) also considers negative lymphovascular space invasion (LVSI) and margin status as criteria for microinvasive disease (MID). The horizontal spread must be 7 mm or less to be considered MID according to FIGO, but SGO does not include lateral spread in defining MID. The diagnosis of MID must be made on a conization or hysterectomy specimen. Punch biopsies are not adequate. Stage IB is divided into IB1, which includes all lesions greater than IA2 and no more than 4 cm in greatest dimension, and stage IB2, a lesion limited to the cervix measuring greater than 4 cm.

Surgical findings and radiographically guided biopsies of suspected lesions cannot be used to change or modify clinical FIGO staging. Stage IVA requires biopsy confirmation of bladder or rectal mucosal involvement. Stage IIIB indicates pelvic sidewall involvement or demonstration of a nonfunctioning kidney or hydronephrosis.

A TNM (Tumor, Node, Metastasis) staging system is proposed by American Joint Committee Commission on Cancer and is mainly used in documenting findings on surgical and pathologic evaluations as the pathologic stage of the disease. If there is ambiguity regarding the correct stage, the lower stage is assigned.

Pretreatment Nodal Staging

The presence of paraaortic lymph node metastases is known to have a significant impact on progression-free and overall survival. Pretreatment knowledge of paraaortic spread could potentially direct treatment in a manner that could improve outcomes. Given the limitations of imaging in reliably detecting paraaortic micrometastases, surgical staging has been used. However, the role of surgical staging for locally advanced cervical cancer remains unclear.

PATHOLOGY

KEY POINTS

- Squamous carcinoma *in situ* (CIS) is a precursor lesion of invasive squamous carcinoma.
- Untreated squamous CIS results in invasive carcinoma in about one third of cases over a period of 10 years.
- Adenocarcinoma accounts for 20% to 25% of cervical carcinomas and is associated with human papillomavirus (usually type 18, but sometimes type 16).
- Adenosquamous carcinomas appear to be either histologically more aggressive or diagnosed at a later stage than adenocarcinomas of the uterine cervix.

Squamous Cell Carcinoma

Preinvasive Disease

Squamous CIS is a precursor lesion of invasive squamous carcinoma, and it is characterized by full-thickness atypia of the cervical epithelium. Endocervical glands may also be involved. The normal maturation of squamous epithelium is absent. There is no breach of the underlying basement membrane.

Microinvasive Carcinoma

Microinvasive squamous carcinoma is associated with squamous intraepithelial neoplasia, and it is characterized by small nests of cells that have escaped the basement membrane of the surface or glandular epithelium. Microinvasive carcinoma often displays cells that are larger, with more abundant eosinophilic cytoplasm than cells in the adjacent dysplasia.

A diagnosis of microinvasive squamous carcinoma of the cervix requires a loop electrosurgical excisional procedure or conization biopsy that encompasses the entire lesion and has negative margins (Fig. 7.1).

Invasive Squamous Cell Carcinoma

Invasive cervical carcinoma arises from high-grade dysplasia, which may be detected up to 10 years before invasive carcinoma develops. Untreated squamous CIS results in invasive carcinoma in about one third of cases over a period of 10 years. Invasive carcinoma occurs most often after the age of 40 years, although it may be seen in young women. It is associated with HPV infection in more than 99% of cases. These tumors may consist of firm, indurated masses, or they may be ulcerated or polypoid. Microscopic examination reveals irregular, haphazardly infiltrating nests of cells with eosinophilic cytoplasm and enlarged, atypical, hyperchromatic nuclei.

Lymphatic and vascular space invasion may be present, especially in more deeply invasive tumors. Invasive squamous carcinomas are also graded, although treatment protocols do not depend on grade, and the histologic grade may not correlate with prognosis. Lesions are graded 1 to 3 or well, moderately, and poorly differentiated. Grade 2 (moderately differentiated) tumors represent the majority of invasive squamous carcinomas of the uterine cervix, and are usually nonkeratinizing squamous carcinomas with nuclear pleomorphism, numerous mitoses, and an infiltrative pattern. Grade 3 (poorly differentiated) tumors either have smaller cells without neuroendocrine differentiation or are pleomorphic with anaplastic nuclei and sometimes a tendency to form spindle cells that must be distinguished from sarcoma by positive cytokeratin stains.

Adenocarcinoma

While the incidence of squamous carcinoma of the cervix has decreased in the past decades owing to cytologic screening, the number of cases of

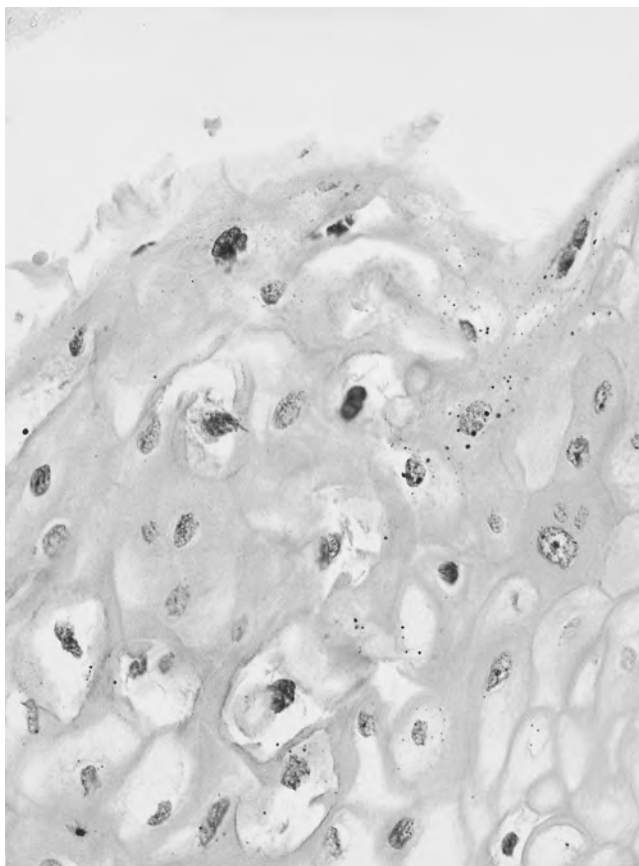


FIGURE 7.1. HPV changes. This squamous epithelium displays cells with large halos surrounding atypical nuclei (“koilocytotic atypia”).

cervical adenocarcinoma has increased. Adenocarcinoma accounts for 20% to 25% of cervical carcinomas.

Adenocarcinoma *in situ* (AIS) is a precursor of invasive adenocarcinoma. It is found adjacent to many invasive adenocarcinomas, often accompanied by squamous dysplasia. Both AIS and invasive adenocarcinoma of the cervix are associated with HPV (usually type 18, but sometimes type 16).

AIS is characterized by preservation of the overall endocervical gland architecture. However, endocervical glands and surface epithelium are replaced to varying degrees by cells displaying atypia. Most adenocarcinomas *in situ* occur near the transformation zone, and skip lesions are unusual.

Other Epithelial Tumors

Adenosquamous carcinoma is a tumor composed of admixed malignant glandular and squamous elements. A recent multi-institutional study found that adenosquamous carcinomas are more commonly associated with higher tumor grade ($p < 0.001$) and vascular invasion ($p = 0.002$) than are adenocarcinomas. Adenosquamous carcinomas appear to be either histologically more aggressive or diagnosed at a later stage than adenocarcinomas of the uterine cervix.

Small Cell Carcinoma

Most neuroendocrine tumors seen in the uterine cervix represent small cell carcinomas. Even a small component of small cell carcinoma in a tumor of mixed type is associated with adverse outcome. These tumors are morphologically identical to those seen in small cell carcinoma of the lung. They are aneuploid tumors that show a strong association with type 18 HPV. Immunohistochemical stains for neuroendocrine markers, such as chromogranin and synaptophysin, may be helpful in the diagnosis. CD56 (neural cell adhesion molecule) is a sensitive marker for the diagnosis of small cell cancer in the cervix.

Mixed Epithelial, Mesenchymal Tumors, and Other Malignant Tumors

Uncommon malignant tumors of the cervix include sarcomas, malignant mixed müllerian tumors, endometrial stromal sarcomas, melanomas, granulocytic sarcomas, primitive neuroectodermal tumors, desmoplastic small round cell tumors, and primary germ cell tumors. Primary extranodal lymphomas of the uterine cervix are usually diffuse B-cell neoplasms.

PROGNOSTIC FACTORS

KEY POINTS

- Size of the primary tumor, depth of stromal invasion, lymphovascular invasion, and parametrial involvement have been correlated with disease-free survival in patients undergoing radical hysterectomy.
- While Fédération Internationale de Gynécologie et d'Obstétrique stage is prognostically significant in predicting outcome, lymph node involvement is, in most studies, the most significant negative prognostic factor.

Tumor Size, Volume, and Margin Status

Size of the primary tumor, depth of stromal invasion, and parametrial involvement have been correlated with disease-free survival in patients

undergoing radical hysterectomy (RH). Lymph-vascular space invasion and depth of cervical stromal invasion have also been associated with significantly poorer prognosis.

Size has also been correlated with increased pelvic failure rates in patients treated definitively with radiation. In patients with stage IB cervical cancer treated surgically, with or without RT, positive margin status conveyed a hazard ratio of 3.92 compared to negative margins. Also, margin status (distance in mm in patients with close margins) was significantly associated with an increased recurrence rate. In this series, postoperative RT eliminated local recurrences in patients with close margins and halved the recurrence rate in patients with positive margins.

Stage

The FIGO stage is universally accepted for its prognostic significance. Paraaortic node metastasis confers a much greater risk than measures of tumor volume, however, and emphasizes the fact that FIGO staging does not take into account important prognostic information such as nodal status.

Nodal Status

Lymph node involvement is, in most studies, the most significant negative prognostic factor. Reports emphasize higher 5-year survival rates (90% or higher) among surgically treated patients with no evidence of metastasis in the regional nodes, compared to patients with positive pelvic (50% to 60%) or paraaortic nodes (20% to 45%).

Lymphovascular Space Invasion

LVSI proved to be a significant prognostic factor in a surgical-pathologic study of 542 patients completed by the Gynecologic Oncology Group (GOG). Disease-free survivals were 77% and 89%, respectively, in patients with and without LVSI. Furthermore, LVSI was shown to correlate with pelvic adenopathy and with time to recurrence.

Hypoxia and Anemia

The presence of both hypoxia and anemia have independently been correlated in multiple studies with adverse outcomes in patients with cervical cancer. The data regarding anemia's impact are largely retrospective, while hypoxia has been studied through direct tumor measurements in patients treated definitely with surgery as well as with radiation therapy. Studies have not confirmed the hypothesis of a direct correlation between anemia and tumor hypoxia, and the relationship between these two prognostic factors is complex.

Several authors have suggested that a lower hemoglobin level could also be a marker for more aggressive disease as opposed to a physiologic variable that could be manipulated for therapeutic benefit.

Histopathology

Conflicting data exist regarding the prognostic significance of adenocarcinoma as compared with squamous cell carcinoma, with some studies suggesting similar survival rates for comparable stages, and others suggesting inferior survival in the adenocarcinoma subgroup. There is evidence that adenosquamous carcinoma is either a histologically more aggressive tumor than cervical adenocarcinoma or it is diagnosed later in the disease course.

Higher tumor grade and vascular invasion are statistically more common in adenosquamous carcinoma than adenocarcinoma of the cervix. The presence of small cell neuroendocrine carcinoma in any amount, even when associated with other types of neoplasm, is an independent prognostic factor associated with aggressive tumor behavior.

GENERAL MANAGEMENT AND RESULTS OF TREATMENT

KEY POINTS

- A quadrivalent vaccine targeting human papillomavirus types 16, 18, 6, and 11 is now recommended for all women of ages 9 to 26 years.
- As up to 30% of cervical intraepithelial neoplasia (CIN) and invasive cancers are caused by strains not in the vaccine, women who receive the vaccine are recommended to be followed according to guidelines already set for cytologic smears.
- Severe dysplasia/CIN and carcinoma *in situ* are adequately managed with local therapies such as conization, laser ablation, cryotherapy, or a simple hysterectomy.
- Stage IA1 carcinoma is usually treated with conization or hysterectomy.
- Stage IA2 squamous cell carcinoma is a modified (type II) radical hysterectomy and pelvic lymphadenectomy, although curative intent RT is an equivalent option.
- Radical surgery and definitive chemoradiation have similar good outcomes for stage IB to IIA nonbulky tumors.
- Bulky IB2, IIB, IIIB, and IVA tumors are treated with curative-intent chemoradiation.

Prevention: HPV Vaccination

The efficacy of the HPV vaccine has been established in randomized clinical trials. A quadrivalent vaccine (QVV) targets HPV types 16, 18, 6,

and 11, and the bivalent vaccine targets types 16 and 18. A double blind placebo-controlled randomized trial evaluating the QVV showed that the combined incidence of persistent infection or disease with the HPV types in the vaccine was reduced by 90%. The Advisory Committee on Immunization Practices, an arm of the CDC, and the American College of Obstetrics and Gynecology have recommended the QVV for all women aged 9 to 26 years. As up to 30% of CIN and invasive cancers are caused by strains not in the vaccine, all women who receive the vaccine are recommended to be followed according to guidelines already set for cytologic smears. The vaccine is given at 0, 2, and 6 months. The vaccine is not effective in women with active HPV infection and abnormal cytology.

Severe Dysplasia and Carcinoma *In Situ*

Patients with severe dysplasia/CIN and CIS have essentially no risk of lymphatic involvement and are often treated with local therapies such as conization, laser ablation, cryotherapy, or a simple hysterectomy. These various techniques have comparable efficacy. Patients with HIV infection, high HPV viral load, positive margins, older age, and residual high-risk infection following conservative management have a higher recurrence rate. Reported rates of recurrent CIS and invasive cancer following therapeutic conization are low (<5%).

Factors associated with persistent disease or invasive cancer following cold knife conization include residual CIN 3, positive ectocervical and endocervical margins, multi-quadrant disease, age more than 50, and positive endocervical curettings. Patients with positive ECC after conization or positive endocervical margins on a cone specimen for CIS should have repeat conization prior to hysterectomy to avoid inappropriate treatment for invasive disease.

Since patients with CIS have virtually no risk of pelvic adenopathy, it is also appropriate to treat with only intracavitary RT. Tumor control rates of 100% have been reported. Grigsby and Perez successfully treated 21 such patients with a single intracavitary implant, delivering a mean point A dose of 46.12 Gy; no treatment sequelae were observed.

Stage IA

The concept of “microinvasion” (equating to FIGO stage IA) should define tumors that penetrate the basement membrane but have little or no risk of nodal involvement or dissemination. All macroscopically visible lesions are considered stage IB tumors.

Stage IA1 carcinoma is usually treated with conization or hysterectomy. The control rate approaches 100%. Absence of LVSI plays a key role in opting for the conservative management of patients with MID as its presence may herald a higher incidence of lymphatic involvement as well as tumor recurrence.

Patients with FIGO IA2 disease with LVSI are not candidates for conservative surgical approaches in most circumstances. The recommended treatment for stage IA2 squamous cell carcinoma is a modified (type II) RH and pelvic lymphadenectomy, although curative intent RT is an equivalent option. The average pelvic lymphatic metastasis rate from reported data is 5% to 13%. In patients who are medically inoperable, intracavitary RT may be used, with several series documenting excellent outcomes and low complication rates.

Adenocarcinoma-Early Disease

The incidence of cervical adenocarcinoma has increased in the past 40 years. Almost all AIS lesions are associated with HPV with 18 being the predominant type. The management of AIS is controversial. The term “microinvasion” may be inaccurate in describing glandular lesions as an accurate measurement of depth of invasion in glands may be difficult. The overall rate of residual disease in hysterectomy specimens after conization with negative margins is 25% and with positive margin is around 50%. Given the critical role of margin status post-conization, a cold knife technique may be preferred in patients with AIS. The recommended surveillance after conization for AIS includes cytology and ECC every 4 months. The most successful conservative management protocols require negative margins and no LVSI, and careful counseling and follow-up are warranted.

Stages IB to IIA (Non-bulky)

Stage IB is divided into IB1 (lesions < 4 cm) and IB2 (lesions confined to cervix > 4 cm). IB1 lesions and selected IIA lesions without extensive vaginal involvement can be treated either with RH and PLD (followed by tailored chemoradiation as indicated by surgical findings) or primary chemoradiation. Surgery is the preferred option in younger women as ovarian function and vaginal length, and thus sexual function, can generally be maintained. Transposition of the ovaries to the abdominal wall or the gutters away from the field of RT may prevent radiation-induced ovarian failure. Retention of ovarian function following ovarian transposition and postoperative radiation has been reported to range from 53% to 71%. The rate of ovarian metastasis is very low, about 0.9%, and thus salpingoophorectomy is not part of RH.

Radical surgery and definitive chemoradiation have similar good outcomes. Typically, 5-year survival for stage IB patients is 85% to 90% and 65% to 75% for stage IIA. In a prospective study of RH ± RT (patients with parametrial involvement, deep stromal invasion, and/or positive nodes received postoperative RT) versus RT alone, no difference was seen in disease-related outcome. In the RH arm, 54% (62 out of 114) and 84% (40 out of 55) of stages IB1 and IB2 received postoperative RT, respectively. Severe morbidity was seen in 28% in the surgical arm (mostly combined surgery and RT) compared to 12% in the RT arm.

Fertility-Sparing Surgery/Radical Vaginal and Abdominal Trachelectomy

Almost 30% of women diagnosed with cervical cancer will be less than 40 years of age and 40% will have early stage I disease. Preservation of fertility can be a major consideration in treatment if an acceptable oncologic outcome can be obtained. Recently, there have been major advances in fertility-sparing surgery (FSS) in women with stage IA2 to IB1 cervical cancers with the introduction of a procedure that involves transvaginal resection of cervical and paracervical tissues (vaginal radical trachelectomy) and proximal vaginal, placement of a permanent cerclage at the cervico-uterine junction, and a laparoscopic pelvic lymphadenectomy.

The overall recurrence rate in the literature is about 4%, comparing favorably with standard treatment. Appropriate lesions include FIGO stage IA1 without extensive LVSI and IA2 or IB1 lesions less than 2 cm with limited endocervical involvement. A review reported that of patients electing FSS, 43% attempt conception, 70% conceive, 49% deliver at term, and 15% have cervical stenosis causing infertility.

Bulky IB Carcinoma of the Cervix

Bulky endocervical tumors and the so-called barrel-shaped cervix cancers have a higher incidence of central recurrence, pelvic and paraaortic lymph node metastasis, and distant dissemination. Historically, adjuvant extrafascial hysterectomy following preoperative RT was an accepted treatment approach

The GOG performed a randomized trial in which 256 eligible patients with carcinomas of the cervix ≥ 4 cm were treated with external beam and intracavitary irradiation, or with a slightly lower dose of intracavitary irradiation and the same external beam pelvic irradiation followed by an extrafascial hysterectomy. The 3-year disease-free survival and overall survival rates were 79% and 83%, respectively, and were virtually identical in the irradiation alone and the combined irradiation and surgery groups. The incidence of progression was somewhat higher in the irradiation alone group (46%) compared to the combined therapy group (37%) ($p = 0.07$). However, it appears that surgery does not contribute to increased survival compared to RT alone in patients with “bulky” stage IB disease.

Stages IIB, IIIB, and IVA

Most patients in the United States with stage IIB disease are treated with curative-intent chemoradiation. With RT alone, the 5-year survival rate has historically been 60% to 65%, and the pelvic failure rate 18% to 39%. Similarly, most patients with stage III and IVA tumors are best treated with concurrent chemoradiation.

Based on multiple randomized clinical trials, concurrent cisplatin is a standard agent to combine with RT. Other chemotherapy agents that have

been used successfully include 5-FU, mitomycin, carboplatin, paclitaxel and epirubicin. Considering all eligible patients with stage IIB to IVA carcinomas enrolled in GOG-85, a 55% survival rate with platinum-based chemotherapy with RT was demonstrated after a median follow-up of 8.7 years. In this same group of patients, GOG-120 found a 66% survival rate with platinum-based chemoradiation.

External Irradiation Alone

Rarely, brachytherapy procedures cannot be performed because of medical reasons or unusual anatomic configuration of the pelvis or the tumor (e.g., extensive lesion and inability to identify the cervical canal, presence of a fistula). These patients may be treated with higher doses of external irradiation alone, although the results are inferior to those obtained with combined external beam and intracavitary irradiation.

UNUSUAL CLINICAL SITUATIONS

Invasive Carcinoma Treated by Simple Hysterectomy

Although uncommon, simple hysterectomy for an unrecognized invasive cervical cancer can occur in patients operated on for what is felt to be CIS, “microinvasive” disease, or for “benign” indications. If only microinvasive carcinoma is found, with no evidence of LVSI, no additional therapy is necessary. However, in patients with more advanced disease, simple extrafascial abdominal hysterectomy is not curative because the paravaginal/paracervical soft tissue, vaginal cuff, and pelvic lymph nodes are not removed.

While technically difficult, an adequate radical operation after previous simple hysterectomy may be appropriate for selected patients. Another approach favored by some is the use of adjuvant pelvic RT in patients with invasive disease of severity greater than microinvasive. In an exhaustive review of the literature comparing series of patients having reoperation with radical parametrectomy and LND versus those having postoperative RT, the weighted average 5-year survivals favored RT (68.7% vs. 49.2%).

If the postoperative RT approach is chosen, postoperative irradiation should be administered immediately after recovery from operation, as prognosis is much worse if therapy is delayed. The potential contribution of concurrent platinum-based chemotherapy must be considered, particularly in view of the randomized study of patients treated after RH with high-risk features (Fig. 7.2).

Small Cell Carcinoma of the Cervix

Small-cell carcinomas account for less than 3% of cervical neoplasms, and are not often confined to the cervix and surrounding tissues at diagnosis.

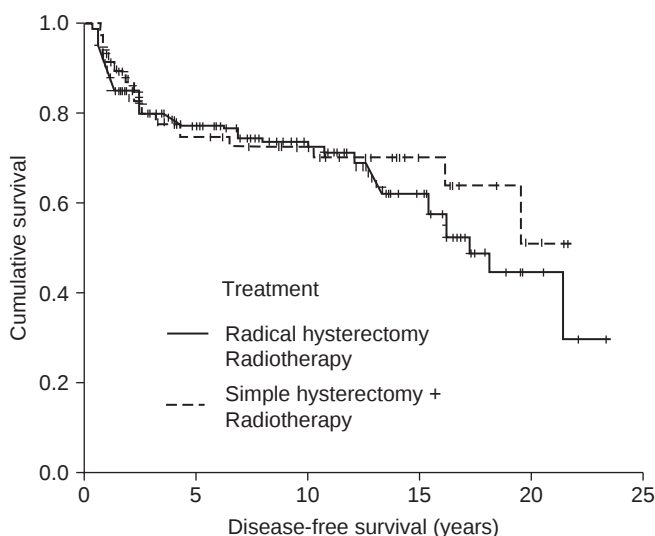


FIGURE 7.2. The influence of type of treatment on disease-free survival in patients undergoing RH with and without RT and those who had simple hysterectomy followed by adjuvant RT. (Kaplan-Meier analysis, p = not significant).

Source: From Munstedt K, Johnson P, von Georgi R, et al. Consequences of inadvertent, suboptimal primary surgery in carcinoma of the uterine cervix. *Gynecol Oncol.* 2004;94:515–520.

Lymph node involvement is present in over 50%, and vascular invasion is frequently present. One small retrospective study suggested no patient with greater than stage IB1 survived, and even for stage IB1 patients, the survival was much worse than would be expected in more common histologies. Given the propensity to distant metastasis, the use of combination chemotherapy has been widely accepted in these patients. Prophylactic cranial RT has also been given following this chemoradiation in the absence of progression.

SURGERY

KEY POINTS

- Class I extrafascial hysterectomy is the most common hysterectomy performed for a variety of gynecologic disorders.
- Class II or modified radical hysterectomy involves resection of the parametrial tissue medial to the ureter and a 1- to 2-cm vaginal margin.
- Class III or radical abdominal hysterectomy involves resection of parametrial tissue to the pelvic sidewall along with a 2- to 3-cm vaginal margin.

A generally accepted classification of types of hysterectomy is given in Table 7.2 and described below.

Class I Extrafascial Hysterectomy

This is the most common hysterectomy performed for a variety of gynecologic disorders. It consists of removing the uterus and cervix with very little removal of vaginal mucosa. This hysterectomy is adequate for the treatment of stage IA1 and advocated by some for stage IA2. This procedure can be accomplished abdominally, vaginally or laparoscopically.

Class II or Modified Radical Hysterectomy

Modified radical hysterectomy (MRH) involves dissection of the uterine artery at its junction with the ureter. The parametrial tissue is resected medial to the ureter. The uterosacral ligaments are isolated, and the proximal portions medial to the ureter are resected. A 1 to 2 cm vaginal margin is resected along with the cervix. A pelvic lymphadenectomy is typically performed along with MRH. Type II MRH is reserved for microscopic or smaller tumors depending on the surgeon's experience and preference.

Class III or Radical Abdominal Hysterectomy

The RH differs from the MRH in the amount of dissection and resection. The ureters are dissected to their insertion into the bladder trigone. The cardinal ligaments are resected to the pelvic sidewall. The uterosacral ligaments may either be dissected to their attachment or in select cases resected midway to their attachment. Resection of 2 to 3 cm of proximal vagina is usual, but the operation can be tailored according to tumor size and patient anatomy.

Class IV or Extended Radical Hysterectomy

There is little indication for extended radical hysterectomy (ERH) with availability of modern RT and chemosensitization for locally advanced tumors. ERH involves complete dissection of the ureter off the vesicouterine ligament, sacrifice of the superior vesical artery, and resection of three fourths of the vagina. The risk of bladder dysfunction and fistula formation is greatly increased compared to type I to III hysterectomies.

Class V Hysterectomy

A rarely performed operation, a type V hysterectomy involves resection of the distal ureter or bladder with reimplantation of ureter if needed.

TABLE 7.2

TYPES OF ABDOMINAL HYSTERECTOMY

Type of Surgery	Intrafascial	Extrafascial Type 1	Modified Radical Type II	Radical Type III
Cervical fascia	Partially removed	Completely removed	→	→
Vaginal cuff removal	None	Small rim removed	Proximal 1–2 cm removed	Upper one third to one half removed
Bladder	Partially mobilized	→	→	Mobilized
Rectum	Not mobilized	R-V septum partially mobilized	→	Mobilized
Ureters	Not mobilized	→	Unroofed in ureteral tunnel	Completely dissected to bladder entry
Cardinal ligaments	Resected medial to ureters	→	Resected at level of ureter	Resected at pelvic sidewall
Uterosacral ligaments	Resected at level of cervix	→	Partially resected	Resected at postpelvic insertion
Uterus	Removed	→	→	→
Cervix	Partially removed	Completely removed	→	→

Note: Type IV, extended RH (partial removal of bladder or ureter), in addition to Type III. (Perez CA. Uterine cervix. In: Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 3rd Ed. Philadelphia, PA: Lippincott-Raven; 1998.)

Source: From Strehman FB, Perez CA, Kurman RJ, et al. Chapter 31—Uterine cervix. In Hoskins WJ, Perez CA, Young RC, eds. *Principles and Practice of Gynecologic Oncology*. 3rd Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2000:864.

Pelvic Exenteration

Total pelvic exenteration (TPE) is mainly used for select stage IVA patients with limited central recurrences and no metastatic disease following treatment with primary RT or combined surgery and RT. It involves *en bloc* removal of bladder, uterus, rectum, vagina, and, at times, vulva, depending on the exact site and extent of recurrence. The procedure can be tailored to remove only the anterior or posterior structures including the bladder (anterior exenteration) or rectum (posterior exenteration). Reported 5-year survivals are approximately 40%, ranging from 18% to 70% in the literature.

Sidewall extension, metastatic disease, and, usually, hydronephrosis are possible contraindications to the procedure. Perioperative complications can include bleeding, infection, cardiac and pulmonary complications, gastrointestinal and urinary leaks, fistulas, bowel obstruction, and reconstruction flap failure. Sexual dysfunction and psychosocial effects are often longer-term sequelae that can be permanent. The mortality rate from TPE is about 5%, even with careful patient selection.

RADIATION THERAPY

KEY POINTS

- Radiation portals are designed to encompass gross disease and regional areas at risk for microscopic spread.
- Extended field radiation therapy (EFRT) can be used either prophylactically or therapeutically to treat the lymph nodes located in the paraaortic chain.
- Results from RTOG 90-01 show that pelvic RT combined with platinum-based chemotherapy is superior to adjuvant EFRT (without chemotherapy) in patients with locally advanced disease and negative paraaortic nodes.
- Chemotherapy can feasibly be added to EFRT in patients with gross metastases to the paraaortic nodes, although at the expense of an increased acute toxicity.
- Brachytherapy allows the delivery of high doses of radiation safely to the tumor and has been a major factor in the ability of RT to cure cervical cancer.
- Standard doses to the whole pelvis with external beam radiation therapy (EBRT) are 40 to 45 Gy, and are combined with one or two low dose rate intracavitary insertions that deliver approximately 40 to 55 Gy to point A, for a total dose of 80 to 90 Gy to point A.
- One recommended high dose rate brachytherapy prescription is 5 fractions of 6 Gy (to point A) in addition to EBRT.

External Irradiation

Standard Fields (Non-Intensity-Modulated Radiation Therapy)

Treatment of invasive carcinoma of the uterine cervix requires delivery of adequate doses of irradiation to the pelvic lymph nodes. The superior border of the pelvic portal should be at the L4–5 interspace to include the external iliac and hypogastric lymph nodes. This margin should be adjusted up or down depending on disease extent (e.g., coverage of common iliac nodes may require the top border to extend to the L2–3 interspace). A 2 cm margin on the AP:PA fields lateral to the bony pelvis is adequate. If there is no vaginal extension, the lower margin of the portal is at the midportion to inferior border of the obturator foramen. When there is vaginal involvement, the field should extend distally beyond the tumor a minimum of 4 cm, although some contend that the entire length of vagina should be treated down to the introitus. It is important to identify the distal extension of the tumor in some manner at the time of initial simulation, for example, by inserting a small rod with a radiopaque marker in the vagina. Often, vaginal extension will not be clearly defined by CT scan. In patients with involvement of the distal third of the vagina, portals should cover the inguinal lymph nodes because of the increased probability of metastases.

The lateral portal anterior margin is placed anterior to the pubic symphysis to include the anterior extent of the external iliac nodes. The posterior margin usually covers at least 50% of the rectum in stage IB tumors, and will often extend to the sacral hollow in patients with more advanced tumors (Fig. 7.3B). Routinely placing the posterior border at the S2–3 interspace (to cover the uterosacral ligament and presacral nodes) frequently results in inadequate coverage of the planning target volume. Ideally, three-dimensional imaging with CT, MRI, or both will be used to ensure adequate coverage.

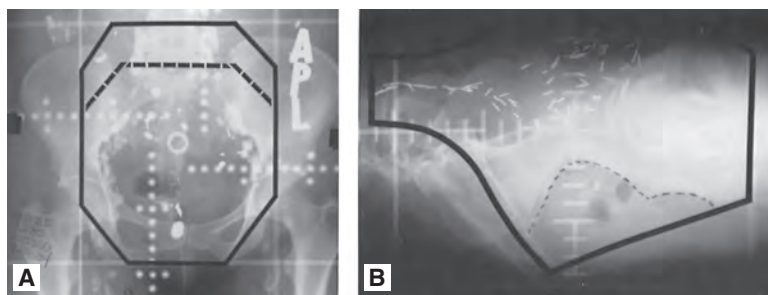


FIGURE 7.3. A: Anteroposterior simulation film of the pelvis illustrating portals used for external irradiation. The 15 × 15 cm portals at SSD (source-skin distance) are used for stage IB (*broken line*), and 18 × 15 cm portals are used for more advanced disease (*solid line*). This allows better coverage of the common iliac lymph nodes. The distal margin is usually placed at the bottom of the obturator foramina. B: Lateral simulation film of the pelvis illustrating portals used for external irradiation.

Source: From Stehman FB, Perez CA, Kurman RJ, et al. Uterine cervix. In: Hoskins WJ, Perez CA, Young RC, et al., eds. *Principles and Practice of Radiation Oncology*. 3rd Ed. Philadelphia, PA: Lippincott-Raven; 2000:867.

Intensity-Modulated External Radiation Therapy

Intensity-modulated radiation therapy (IMRT) refers to the delivery of radiation beams with varying intensity patterns that create a dose distribution, which covers the target with the prescribed dose while limiting doses to normal surrounding structures. Treatment planning is based on three-dimensional imaging utilizing CT, most commonly. MRI and PET images can be fused with planning CT scans to more accurately delineate the treatment volume (Fig. 7.4).

Potential benefits of IMRT include the ability to preferentially limit the dose of radiation to normal tissues, safely deliver higher tumor doses,

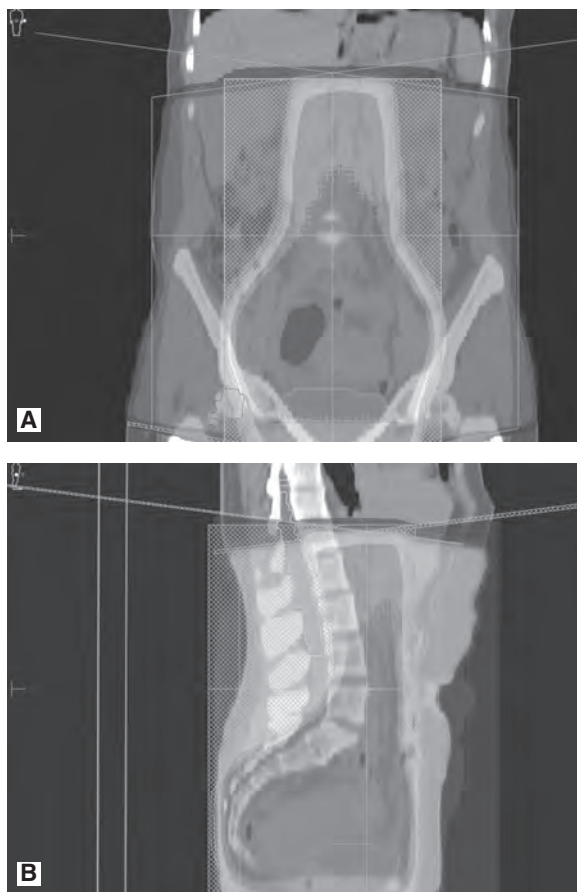


FIGURE 7.4. This shows dose distribution from extended field RT given with a four-field isocentric technique with all fields treated in continuity. The AP-PA fields (A) are weighted 70:30 in relation to the lateral fields (B), limiting the dose to kidneys, as shown in the DVH in Figure 7.4 This patient had a large pelvic mass, compromising the ability to spare rectum and bladder.

and enable treatment and retreatment of tumors that are not otherwise treatable. To date, the weight of opinion does not support the ability of IMRT techniques to replace intracavitary brachytherapy for the treatment of cervical cancer.

A concern and possible pitfall from the implementation of IMRT for gynecologic cancers include the problem of organ and tissue motion. Other concerns include an increase in the incidence of secondary radiation-induced malignancies, limitations of imaging in accurately defining pelvic disease, increased dose heterogeneity, and problems with quality assurance.

Extended Field Radiation Therapy

Extended field radiation therapy (EFRT) can be used either prophylactically or therapeutically to treat the lymph nodes located in the paraaortic chain. The paraaortic chain is surrounded by organs of limited radiation tolerance, that is, spinal cord, kidneys, and small intestine, and thus concerns regarding its use relate to increased acute and late toxicities. Conventional techniques for treatment include the use of opposed anterior and posterior fields and a four-field technique (AP:PA and opposed laterals). Careful determination of kidney location with an intravenous pyelogram (IVP) or CT scan and knowledge and respect of normal tissue tolerance limits (kidneys, small bowel, and spinal cord) are critical when designing fields and beam weighting. A dose-volume histogram (DVH) of such a treatment is shown in Figure 7.5.

Elective Paraaortic Lymph Node Irradiation

Occult involvement of the paraaortic lymph nodes is a potential cause of treatment failure in carcinoma of the cervix. Adjuvant or EFRT is a logical treatment strategy that seeks to avoid the risks and treatment delays associated with surgical staging. Retrospective and prospective data suggest that EFRT can be delivered safely and with reasonable efficacy in high-risk patients. In a prospective RTOG trial that randomized 367 patients (stage IIB or stages IB to IIA, 4 cm) to pelvic RT versus EFRT, elective EFRT translated into overall survival of 67% at 5 years, and 55% at 10 years compared with 55% and 44%, respectively, for those treated to the pelvis only ($p = 0.02$). Loco-regional failures were similar at 10 years for both arms (pelvic only, 35%; EFRT, 31%). When the first disease failure patterns were examined, more patients failed distally when treated only with pelvic RT compared to those receiving EFRT ($p = 0.053$). The EFRT arm was associated with more grade 4 and 5 complications, particularly in patients with prior abdominal surgery (11% vs. 2%).

Results from RTOG 90-01 show that pelvic RT combined with platinum-based chemotherapy is superior to adjuvant EFRT (without chemotherapy) in patients with locally advanced disease. EFRT combined with chemotherapy could offer opportunities for improved outcomes in patients at high risk of metastatic paraaortic disease.

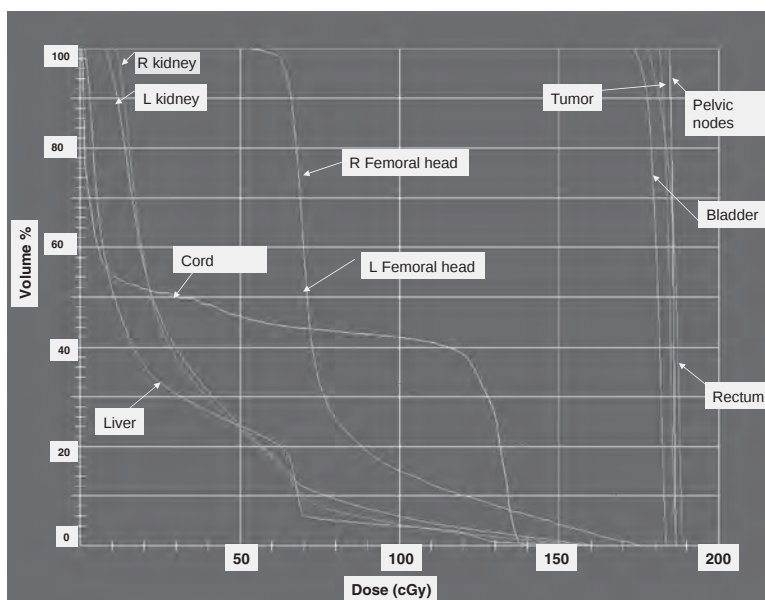


FIGURE 7.5. This DVH from an extended field RT plan plots the volume of various organs or structures versus the dose received. It shows excellent coverage of tumor and nodal regions while the normal structures, for example, kidneys, spinal cord, etc., receive limited dose. This provides quantitative measures of dose distribution for use in evaluating and comparing treatment plans.

Possible indications for consideration of EFRT include positive PET scans in the paraaortic region; high pelvic lymph nodes involved, for example, common iliac; gross nodal metastases in pelvis; bilateral positive pelvic lymph nodes; adenocarcinoma histology with any number of positive pelvic lymph nodes; and squamous cell histology with four positive pelvic lymph nodes.

Therapeutic Paraaortic Lymph Node Irradiation

Data from the GOG suggest that patients with stage IB, II, III, and IVA cervical cancers will have spread to the paraaortic lymph nodes in 5%, 16%, 25%, and 13%, respectively. Tumor involvement in paraaortic lymph nodes is quite uncommon in the absence of pelvic lymph node metastasis. The degree to which RT demonstrates curative potential in this group of patients is quite variable, and is mostly related to selection factors in the patient population so treated.

Therapeutic EFRT in patients with paraaortic metastases appears to be efficacious, resulting in long-term survivals of 25% to 50%. Chemotherapy can feasibly be added to EFRT in these patients, although at the expense of increased acute toxicity. While the optimum chemotherapy agents and

schedule remain to be determined, weekly cisplatin is a reasonable suggestion based on current knowledge.

Brachytherapy

Brachytherapy refers to the placement of radioactive sources at a short distance from the intended target. Brachytherapy allows the delivery of high doses of radiation safely and has been a major factor in the ability of RT to cure cervical cancer. For details on brachytherapy, please refer to Chapter 2.

Doses of Irradiation

Invasive carcinoma of the cervix is treated with a combination of whole pelvis and intracavitary therapy. Standard doses to the whole pelvis with external irradiation are 40 to 45 Gy, delivered by four-field box or IMRT technique. This is usually combined with one or two low dose rate (LDR) intracavitary insertions for approximately 40 to 55 Gy to point A, depending on tumor stage (volume). Usual doses to point A from both the external irradiation to the whole pelvis and the LDR intracavitary brachytherapy range from 70 Gy for small (1 cm) stage IB tumors to 90-Gy for stage IIB or IIIB tumors. In some patients, an additional parametrial dose is administered in patients with IIB, III, or IVA tumors (considering the dose delivered to the side wall by the brachytherapy). The recommended high dose rate (HDR) brachytherapy prescription in GOG cervical cancer protocols is 5 fractions of 6 Gy (to point A) in addition to external beam radiation therapy (EBRT).

Overall Treatment Time

Several studies have demonstrated lower pelvic tumor control and survival rates after definitive RT in invasive carcinoma of the uterine cervix when the overall treatment time is prolonged. Combining the published results, one can suggest that pelvic control will suffer at an approximate rate of 1% per day that treatment extends beyond 52 days. This impact will be potentially seen in all stages of localized disease, and survival will be negatively affected.

CHEMOTHERAPY

Chemotherapy is increasingly utilized in the management of cervical cancer, both in primary management and for recurrent and metastatic disease. Conventional agents that are able to induce a response rate of at least 20% in measurable disease include cisplatin, paclitaxel, topotecan, ifosfamide, doxorubicin, epirubicin, and vinorelbine. Doublets that combine these agents with cisplatin result in a doubling of response rate and improved

progression-free survival but little or no improvement in overall survival when compared to cisplatin as a single agent. Three and four drug chemotherapy regimens further increase the response rate without improvement in overall survival at the expense of increased toxicity.

COMBINED MODALITY TREATMENT

Adjuvant Hysterectomy after Radiation Therapy

The main impetus for adjuvant hysterectomy post-radiation therapy (AHPRT) is to decrease the incidence of pelvic recurrence; however, its use remains controversial because overall survival appears to be unaffected. A randomized trial to address this question was performed by the GOG in 256 patients with cervix cancers more than 4 cm in size who were randomized to curative doses of pelvic RT with brachytherapy versus preoperative doses of RT and brachytherapy plus AHPRT. The relapse rate was significantly lower in the AHPRT arm versus RT alone (27% vs. 14%). The incidence of progression was somewhat higher in the RT alone group at 46% versus in 37% ($p = 0.07$) in the AHPRT group. However, no overall survival advantage was seen, and the toxicities were similar in both groups.

Adjuvant Postoperative Pelvic RT

KEY POINTS

- Two groups of patients with early-stage cervical cancer warrant treatment with postoperative radiation: those with intermediate risk features (presence of two out of three risk factors of large tumor size, lymphovascular invasion, and deep stromal invasion) and those with high-risk features (positive nodes, margins, or parametria).
- A phase III GOG trial in women with intermediate risk cervical cancer treated with radical hysterectomy (RH) ± RT showed a 46% reduction in the risk of recurrence in the RT arm compared to the observation arm ($p = 0.007$) and a reduction in the risk of progression or death ($p = 0.009$).
- A phase III Intergroup trial in high-risk women treated with RH and postoperative radiation ± chemotherapy showed a significant improvement in 3-year survival with concurrent cisplatin/5-fluorouracil and irradiation followed by adjuvant chemotherapy compared with pelvic irradiation alone (87% vs. 77%, respectively).
- An ongoing randomized cooperative group trial is presently investigating the benefit of adjuvant carboplatin and taxol chemotherapy following postoperative chemoradiation in women with early-stage high-risk cervical cancer.

The most common failure pattern following radical surgery for cervical carcinoma is pelvic relapse. Based on an extensive GOG clinico-pathologic study, recommendations were made to separate patients into intermediate- and high-risk groups. Intermediate-risk criteria relate to tumor size, depth of stromal invasion, and LVSI. High-risk criteria include positive pelvic nodes, close or positive margins, and parametrial extension. Retrospective and prospective data suggest that adjuvant pelvic RT significantly improves pelvic control rates and disease-free survivals in patients with risk factors for recurrence who have completed radical surgery. The role of chemotherapy, particularly in high-risk patients, has also become established.

Intermediate Risk, Node Negative

The GOG conducted a Phase III trial comparing RH alone with RH and postoperative pelvic RT in patients with node-negative stage IB cervical carcinomas, with prognostic features correlated with an intermediate risk of recurrence (GOG-92). Eligibility criteria for this study are given in Table 7.3. There were 277 patients randomized after RH: 137 to pelvic RT and 140 to no further therapy. RT consisted of 46 Gy to a whole pelvic field. No brachytherapy was used. After a median follow-up of 5 years for living patients, recurrence was observed in 28% of the patients in the control group, and in 15% of the radiated patients. There was a statistically significant reduction in the risk of recurrence (relative risk = 0.53, $p = 0.008$) in the irradiated group. Severe or life-threatening adverse effects were observed in 7% of the radiated patients, versus 2.1% of the controls. After additional follow-up and data maturation, a final report from GOG-92 showed a 46% reduction in the risk of recurrence in the RT arm compared to the observation arm ($p = 0.007$) and a reduction in the risk of progression or death ($p = 0.009$). Particularly striking was the impact of postoperative RT in patients with adenocarcinoma or adenosquamous histologies: among this subset, only 8.8% recurred in the RT arm as against 44% in the observation arm. There was a strong trend

TABLE 7.3

GOG-92 ELIGIBILITY CRITERIA

Capillary Lymphatic Space Involvement	Stromal Invasion	Tumor Size
Positive	Deep 1/3	Any
Positive	Middle 1/3	≥2 cm
Positive	Superficial 1/3	≥5 cm
Negative	Deep or middle 1/3	≥4 cm

toward improved survival in the RT arm, but this did not reach statistical significance ($p = 0.074$).

Management of patients with stage IB2 tumors is somewhat controversial, in that some favor initial surgery followed by adjuvant RT, while others recommend curative intent chemoradiation, avoiding the use of two local modalities.

Node-Positive/High-Risk Patients

Metastatic disease in the pelvic lymph nodes is a poor prognostic sign. An intergroup study was conducted by the Southwest Oncology Group (SWOG), GOG, and RTOG in women with FIGO stages IA2, IB, or IIA carcinoma of the cervix found to have metastatic disease in the pelvic lymph nodes, positive parametrial involvement, or positive surgical margins at time of primary radical hysterectomy, and total pelvic lymphadenectomy with confirmed negative paraaortic lymph nodes. One hundred twenty-seven patients were randomized between pelvic external beam radiation therapy with 5-FU infusion and cisplatin, and 116 were treated with pelvic external beam irradiation alone. The median follow-up for survivors was 43 months. Three-year survival was significantly improved with concurrent cisplatin/5-fluorouracil and irradiation followed by adjuvant chemotherapy compared with pelvic irradiation alone (87% vs. 77%, respectively). Chemotherapy appeared to reduce both pelvic and extrapelvic recurrences.

Close or Positive Margins/Parametrial Involvement

Eighty-five percent of patients accrued on the SWOG/GOG/RTOG Intergroup study were eligible based on pelvic node involvement. Only 5% of patients accrued to this intergroup study had positive margins. Nevertheless, patients with positive or close margins and/or parametrial involvement are considered to be at high risk and, based on this randomized trial, should be considered for adjuvant chemoradiation.

Radiation Therapy Dose and Technique

Vaginal intracavitary RT alone can be appropriate for patients with CIS with minimally invasive carcinoma at the vaginal margin of resection as the only risk factor. Outpatient HDR brachytherapy is commonly employed because it prevents the prolonged immobilization required for LDR brachytherapy. The usual dose per fraction prescribed at 0.5 cm depth is 7 Gy; three weekly fractions are typically given. The upper 3 to 5 cm of the vagina should be targeted.

When external RT is used, patients generally should not receive more than 45 Gy to the whole pelvis. Doses up to 50.4 Gy are acceptable when treating smaller fields that exclude more small bowel. Brachytherapy or small-field external beam boosts can be given, within tolerance, to increase dose to the central pelvis.

The use of IMRT with chemotherapy has been reported to maintain excellent pelvic control rates, with better acute tolerance and fewer chronic toxicities compared to conventional four-field box RT.

Chemotherapy in Combinations for Localized Carcinoma of the Cervix Neoadjuvant Chemotherapy Followed by Radiotherapy

Randomized trials of neoadjuvant chemotherapy (NACT) followed by radiation versus radiation alone in patients with locally advanced cervical cancer (mainly stages III and IV) have been disappointing, in terms of both complete response rates and increase in survival. A meta-analysis of 18 randomized clinical trials of neo-adjuvant chemotherapy including 2074 patients compared NACT followed by RT to RT alone and demonstrated no advantage of neo-adjuvant chemotherapy with regard to progression-free survival, loco-regional disease-free survival, metastasis-free survival, or overall survival. NACT followed by RT for patients with locally advanced cervical cancer should not be performed based on existing data.

Neoadjuvant Chemotherapy Followed by Surgery

Numerous nonrandomized studies reported in the 1990s suggested that NACT followed by surgery might be an attractive approach, and some but not all of the randomized trials show a trend in favor of this combined approach. A meta-analysis of five randomized clinical trials and 872 patients who received NACT followed by surgery $\pm$ RT was compared to RT alone. There was a significant improvement in progression-free survival, loco-regional disease-free survival, metastasis-free survival, and overall survival for those who were resectable following NACT. Nevertheless, based on the available data, NACT remains investigational.

Adjuvant Chemotherapy

Several nonrandomized studies suggest a beneficial effect of adjuvant chemotherapy given after radical surgery in patients at high risk for recurrence. Two randomized trials with a very limited number of patients have tried to evaluate the effect of adjuvant chemotherapy in patients with high-risk cervical cancer after RH. The results of both studies were inconclusive. An ongoing randomized cooperative group trial is presently investigating the benefit of adjuvant carboplatin and taxol chemotherapy following postoperative chemoradiation in women with early-stage high-risk cervical cancer.

TREATMENT OF RECURRENT CARCINOMA OF THE CERVIX

The main cause of death among women with cervical cancer is uncontrolled disease in the pelvis. However, a subset of patients with recurrent disease confined to the pelvis following definitive therapy, whether that therapy is surgery or RT, is potentially curable.

When curative-intent salvage treatment is contemplated, the local recurrence should be biopsy proven, and the patient should be evaluated for regional and distant metastases by physical examination and imaging. PET scanning may be the most accurate test in terms of assessing metastasis prior to embarking on local salvage therapy. Generally, patients with pelvic or regional recurrences after definitive surgery alone are managed with RT or chemoradiation, often with brachytherapy. Salvage options for patients with central recurrence after definitive or adjuvant RT are limited to radical, usually exenterative, surgery, and in selected patients, re-irradiation using interstitial radiation implants or highly conformal EBRT or IMRT. Chemotherapy-responsive patients can obtain meaningful palliation in many cases (Table 7.4).

COMPLICATIONS AND SEQUELAE OF TREATMENT

KEY POINTS

- Complications following radical hysterectomy include ureteral injuries, vesico-vaginal or ureterovaginal fistulas (1% to 2% of cases), bladder atony (5%), lymphocyst formation (1.6%), and lymphedema (3.6%).
- Grade 2 or higher late sequelae of pelvic RT occur in 5% to 15% of cases and may include chronic proctosigmoiditis, rectal stricture, rectal ulcer, bowel obstruction, malabsorption syndrome, chronic cystitis, bladder contracture, urethral stricture, incontinence, vaginal stenosis/fibrosis, dyspareunia, vault necrosis, and rectovaginal or vesicovaginal fistulae.
- Concurrent chemoradiation results in additional acute hematologic toxicity although most phase III studies show no significant increase in late toxicity.

Surgery Related

The most common complications with conization include infection, bleeding, damage to surrounding structures (bladder, rectum, and vagina), and cervical incompetence with predisposition to preterm labor in future pregnancies. RH and lymphadenectomy may result in additional and

TABLE 7.4

**RANDOMIZED STUDIES OF CISPLATIN-BASED COMBINATIONS
VERSUS SINGLE-AGENT CISPLATIN IN PATIENTS WITH
CERVICAL CANCER**

Arms of Studies and Study Drug	No. of Patients	CR <i>n</i> (%)	PR <i>n</i> (%)	CR + PR <i>n</i> (%)	Median Survival (months)
MMC/VCR/ BLM/CDDP	54	4 (7)	8 (15)	12 (22)	6.9
<i>vs.</i>					
MMC/ CDDP	51	2 (4)	11 (21)	13 (25)	7
<i>vs.</i>					
CDDP	9	1 (11)	2 (22)	3 (33)	17
DVA/BLM/ MMC/ CDDP	143	11 (8)	33 (23)	44 (31) ^b	10
<i>vs.</i>					
CDDP	144	8 (6)	20 (14)	28 (19) ^b	9.4
DBD/ CDDP	153 (147) ^a	14 (9)	17 (12)	31 (21)	7.3
<i>vs.</i>					
IFOSF/ CDDP	155 (151) ^a	19 (12.5)	28 (18.5)	47 (31) ^c	8.3
<i>vs.</i>					
CDDP	146 (140) ^a	9 (6.5)	16 (11.5)	25 (18) ^{Pc}	8
BLM/IFOSF/ CDDP	50 (46) ^a	12 (26)	12 (26)	24 (52) ^d	8
<i>vs.</i>					
CDDP	56 (51) ^a	5 (10)	10 (20)	15 (29) ^d	6

^aNumbers evaluable for response.

^b*p* = 0.03.

^c*p* = 0.004.

^d*p* < 0.01.

CR, complete response; PR, partial response; MMC, mitomycin C; VCR, vincristine; BLM, bleomycin; CDDP, cisplatin (dose in all studies and in all arms 50 mg/m²); DVA, vindesine; DBD, dibromodulcitol; IFOSF, ifosfamide.

somewhat unique complications. Urologic complications, such as ureteral injuries and vesico-vaginal or ureterovaginal fistulas, are reported in 1% to 2% of cases, and this can be increased in patients requiring postoperative RT. The majority of vesico-vaginal fistulas will heal spontaneously with continuous bladder drainage for 6 to 8 weeks and treatment of any underlying infection. Conservative management of ureterovaginal fistulas can include ureteral stenting and drainage of the urinary system via percutaneous nephrostomy, which may lead to healing of the fistula. Surgical repair of fistulas may be required for those that do not resolve with conservative management. Fistulas that occur following pelvic RT are less likely to heal with conservative management and may require earlier surgical treatment. As surgical repair after RT has a lower success rate, urinary diversion may be required as definitive treatment.

Lymphocyst formation is about 1.6% and the lymphedema rate is about 3.6% following pelvic LND. Located over the sacral promontory, the hypogastric plexus contains sympathetic fibers that fuse with parasympathetic fibers located in the parametrium and allows for bladder contraction and compliance. Surgical disruption of this plexus results in bladder atony and dysfunction in about 5% of patients, possibly requiring continuous or intermittent drainage for a few weeks.

Rectal function can also be impacted by RH. In a study utilizing a questionnaire to evaluate rectal function after RH in 48 patients, 18% had constipation, 33% required chronic straining, and 60% required laxative or manual assistance with defecation. The incidence of chronic constipation was more than 20%.

Radiation Therapy Related

Acute effects during external pelvic RT most typically include diarrhea and bladder irritation. These are usually self-limited and can be managed effectively with conservative measures. Most late gastrointestinal and urologic complications occur within the first 3 years after RT, with an overall fistula rate of about 2%. Factors that may increase the rate of fistula are combined treatment (surgery and RT), smoking, thin habitus, inflammatory bowel diseases, and diabetes and other vasculopathies.

Commonly reported late sequelae of pelvic RT by site are as follows:

1. Recto-sigmoid complications: chronic proctosigmoiditis, rectal stricture, and rectal ulcer.
2. Small intestine complications: obstruction and malabsorption syndrome.
3. Genitourinary (GU) complications: chronic cystitis, bladder contraction, urethral stricture, and incontinence.
4. Vaginal complications: vaginal stenosis/fibrosis, dyspareunia, vault necrosis, and rectovaginal or vesicovaginal fistulae.

There is approximately a 5% rate of major late sequelae in patients with stage I cervical carcinoma treated with RT, and approximately 10% in

patients with stage II to IVA diseases. Grade 2 complications are seen in 10% to 15% of patients with all stages treated with RT alone. Risk is related to a number of factors, mainly dose and volume treated. A greater incidence of pelvic complications has been consistently observed in patients treated with higher doses to the whole pelvis (above 40 to 50 Gy). Injury to the gastrointestinal tract is the most frequent late complication of RT for cervical cancer.

Combined Modality Related

Irradiation Followed by Surgery

One larger retrospective series of patients with stage IB cervical carcinoma treated with RT reported an incidence of major complications at 3 and 5 years of 7.7% and 9.3%; the actuarial risk of major complications was 14.4% at 20 years. The rate of fistula formation was doubled in those who underwent adjuvant hysterectomy (5.3% vs. 2.6%).

In a GOG study, 256 patients with stage IB carcinomas of the cervix—4 cm confined to cervix—were treated either with external RT and intracavitary irradiation or with external RT and a lower dose of intracavitary irradiation followed by an extrafascial hysterectomy. The toxicities were similar in both groups with grade 3 and 4 toxicities of about 10% in each arm.

Surgery Followed by Irradiation

Radical surgery commonly results in intestinal adhesions to denuded surfaces in the pelvis. When postoperative RT is given, complications are

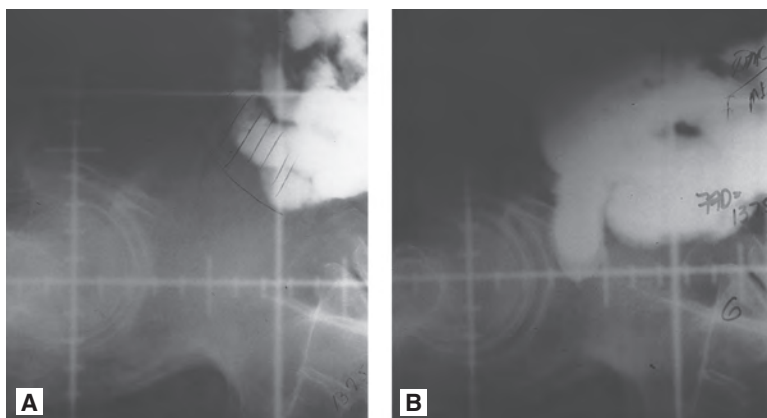


FIGURE 7.6. A,B: Lateral radiographs with and without bladder distention in a patient with contrast in small intestine.

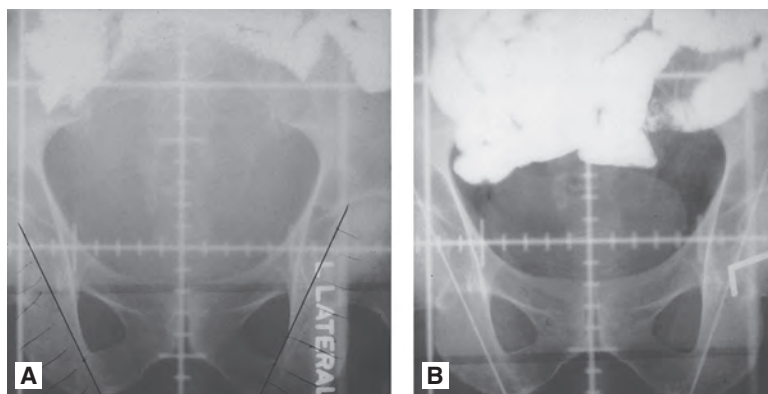


FIGURE 7.7. A,B: Anterior–posterior radiographs with and without bladder distention in a patient with contrast in small intestine.

more likely. The Gynecologic Oncology Group demonstrated a significant increase in grade 2 late complications among patients undergoing pre-RT surgical staging, particularly with a transperitoneal approach compared with a retroperitoneal approach. Pretreatment laparotomy also increased the rate of fistula formation (5.2% vs. 2.9%) as well as small bowel obstruction (14.5% vs. 3.7%). An extraperitoneal approach to lymph node staging lessens these complications.

In a randomized study of postoperative RT versus no further treatment (NFT) after RH, grade 3 to 4 GU toxicities were noted in 3.1% versus 1.4% in the RT as compared to the NFT arm, respectively. Similarly, grade 3 and 4 GI toxicities were 3.1% versus 0.8%, respectively. Overall grade 3 and 4 toxicities were 6% in the RT group versus 2.1% in the NFT arm.

Methods to decrease the volume of small bowel irradiated will further lessen enteric morbidity. Figures 7.6 and 7.7 show the effect of treating patients in the prone position with a full bladder as a means of limiting the volume of small bowel irradiated. Similarly, IMRT techniques can also be used to limit doses to normal tissues.

Concurrent Chemoradiation

Concurrent chemoradiation results in additional acute hematologic toxicity. A major concern has been the possible need to delay treatment, thus potentially compromising outcomes. Typical RT fields radiate some pelvic bone marrow, and the use of IMRT to limit hematologic toxicity in some patients is currently being investigated.

Although some early series suggested that concurrent chemotherapy increased late complications in patients receiving curative intent RT, most studies suggest no significant impact.

Thromboembolic Complications

Thromboembolic complications were reported in a series of 281 consecutive patients who underwent radical surgery for cervical and uterine malignancies. Postoperative thromboembolic complications occurred in 7.8% of patients despite regular use of low dose heparin and antiembolism stockings during the postoperative hospitalization. A second series noted a 16.7% incidence of thromboembolic complications in 48 patients who received chemoradiation therapy without surgery. Brachytherapy alone is associated with a very low rate of thromboembolic complications: 0.3% in one series.

Erythropoietin has been utilized to maintain normal hemoglobin levels during chemoradiation. Reports of increased incidence of thromboembolic complications have been noted in patients who receive erythropoietin during RT. The routine use of erythropoietin to maintain normal hemoglobin levels during chemoradiation should be discouraged.

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CHAPTER 8 ■ THE CORPUS: EPITHELIAL TUMORS

There will be an estimated 42,160 new cases and 7,780 deaths due to endometrial carcinoma in the United States in 2009. Factors influencing its rising incidence include prolonged life expectancy, earlier diagnosis, and worsening national obesity. Currently, endometrial adenocarcinoma is the fourth most common cancer in females, behind breast, colorectal, and lung cancers. It is the seventh leading cause of death from malignancy in women. The lifetime risk of endometrial cancer is 2.6% among American women with a 0.5% lifetime mortality risk.

In 75% of all cases, the tumor is confined to the uterine corpus at the time of diagnosis, and survival rates of 75% or more are expected. In the past 50 years, the treatment of this cancer has evolved from a regimen of preoperative radiation therapy followed 6 weeks later by hysterectomy, to individualized management of hysterectomy and surgical staging as primary therapy with additional treatment depending on various risk factors. In 1988, this operative approach led the International Federation of Gynecology and Obstetrics (FIGO) to require surgical staging for the primary treatment of uterine carcinoma. In 2009, FIGO revised the staging for endometrial carcinoma (Table 8.1).

In the past 30 years, a number of chemotherapeutic regimens have been tested as adjuvant treatment in the primary setting or for recurrent disease. The administration of chemotherapeutic agents to patients with unresectable or recurrent disease remains largely palliative, and novel approaches are under investigation. Adjuvant chemotherapy for uterine serous carcinomas is gaining wider acceptance, yet prospective trials are currently lacking. Though most carcinoma of the endometrium is easily diagnosed, well-differentiated cancers may be difficult to separate from advanced atypical hyperplasia.

EPIDEMIOLOGY AND RISK FACTORS

KEY POINTS

- Type I cancers are estrogen related and Type II cancers are more aggressive.
- Tamoxifen increases the risk of endometrial cancer, but its benefit for breast cancer outweighs this risk.
- Complex atypical hyperplasia has a high incidence of containing a coexistent invasive lesion.

TABLE 8.1

FIGO STAGING OF CARCINOMA OF THE ENDOMETRIUM
(UPDATED 2009)

Stage 1	Tumor Confined to the Corpus Uteri
IA ^a	No or less than half the myometrial invasion
IB ^a	Invasion equal to or more than half of the myometrium
Stage II ^a	Tumor invades cervical stroma, but does not extend beyond the uterus ^b
Stage III ^a	Local and/or regional spread of the tumor
IIIA ^a	Tumor invades the serosa of the corpus uteri and/or adnexae ^c
IIIB ^a	Vaginal and/or parametrial involvement ^c
IIIC ^a	Metastases to pelvic and/or paraaortic lymph nodes ^c
IIIC1 ^a	Positive pelvic nodes
IIIC2 ^a	Positive paraaortic lymph nodes with or without positive pelvic lymph nodes
Stage IV ^a	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA ^a	Tumor invasion of bladder and/or bowel mucosa
IVB ^a	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

^aEither G1, G2, or G3.^bEndocervical glandular involvement only should be considered as stage I and no longer as stage II.^cPositive cytology has to be reported separately without changing the stage.**Source:** From Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009;105:103–104.

Two broad histologic categories of endometrial cancer exist (Table 8.2). Type I cancers are those arising from increased levels of circulating estrogen, and Type II cancers are mostly unrelated to hormonal events. Type I cancers usually occur at a younger age and are less aggressive. Risk factors associated with increased circulating estrogen are typically associated with an increased risk of endometrial cancer, and vice versa. Diabetes and hypertension, once thought to be risk factors for endometrial cancer, are most likely surrogates for obesity and are unlikely to be important

TABLE 8.2**COMPARISON BETWEEN TYPE I AND TYPE II
ENDOMETRIAL CANCERS**

	Type I	Type II
CLINICAL FEATURES		
Risk factors	Unopposed estrogen	Age
Race	White > black	White = black
Differentiation	Well differentiated	Poorly differentiated
Histology	Endometrioid	Nonendometrioid
Stage	I/II	III/IV
Prognosis	Favorable	Not favorable
MOLECULAR FEATURES		
Ploidy	Diploid	Aneuploid
K-ras overexpression	Yes	Yes
Her-2/neu overexpression	No	Yes
P53 overexpression	No	Yes
PTEN mutations	Yes	No
MSI	Yes	No

independent risk factors. Obesity and family history remain two of the strongest risk factors for endometrial cancer.

The molecular defects associated with endometrial cancers are stratified between Type I and Type II cancers. Type I cancers frequently have PTEN, KRAS, and PIK3CA mutations and this is also varied by race, whereas Type II cancers are more likely to have TP53 mutations. Among women belonging to families with the autosomal dominant hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, the most common extra-colonic malignancy is endometrial carcinoma with a lifetime risk of 40% to 60%.

Tamoxifen is a key drug in the treatment and prevention of breast cancer. It is well known to be associated with an increased risk of endometrial cancer as it has agonist properties in the uterus and antagonist properties in the breast. Since the initial report by Killackey et al., the risks of endometrial cancer associated with tamoxifen have been well delineated through the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 and B-14 trials. Overall, the risk of endometrial cancer appears to be low, with the vast majority of cancer occurring as stage I tumors of epithelial histology. The annual rates of endometrial cancer in the placebo group from the NSABP P-1 trial were 0.7/1,000 and 2.2/1,000 for the tamoxifen-treated group. The relative risk of an endometrial cancer occurring in the randomized, tamoxifen-treated

group was 3.3 (95% CI: 1.9, 6.0). These rates are similar to those seen in the NSABP B-14 trial. The main increase in risk seemed to be limited to women over 50 years of age. There have been reports suggesting that uterine sarcomas develop with greater frequency in women taking tamoxifen. Though this may be true, the actual incidence of these cancers is extremely low and does not warrant particular intervention directed toward this phenomena.

Specifically, it is important to note that the benefits of tamoxifen in reducing breast cancer recurrence and new contralateral breast cancers far outweigh the risks of endometrial cancer. As well, there is no evidence to support screening with ultrasound or biopsy for endometrial cancer in women taking tamoxifen. These women should be counseled to promptly report abnormal vaginal bleeding, which should be thoroughly evaluated. The issue of hysterectomy in women taking tamoxifen is controversial, but most authorities would agree that a prophylactic hysterectomy solely for reducing the risk of tamoxifen-associated endometrial cancer is not warranted.

PRE-INVASIVE DISEASE

The current classification of endometrial hyperplasia accepted by both the International Society of Gynecologic Pathologists (ISGP) and the World Health Organization (WHO) is based on the schema of Kurman et al., which divides hyperplasia on the basis of architectural features into simple or complex, and on the basis of cytologic features into typical or atypical. The resulting classification has four categories as follows: simple hyperplasia (SH), complex hyperplasia (CH), simple atypical hyperplasia (SAH), and complex atypical hyperplasia (CAH). The justification for this classification system rests on three retrospective studies that demonstrate a high rate of progression of CAH to adenocarcinoma.

Three articles recently have addressed the reproducibility of diagnoses of hyperplasia. Intraobserver reproducibility was generally found to be moderate to good, while interobserver reproducibility was poor to moderate for various diagnostic categories. In a currently active study by the Gynecologic Oncology Group (GOG), the ability to confirm a community-based diagnosis of atypical hyperplasia by means of an expert panel of pathologists is being evaluated. The current classification of hyperplasia relies on a combination of multiple architectural and cytologic criteria. Coexistent adenocarcinoma may be present in up to 40% of hysterectomies performed to treat CAH. There are reasonably good data to support that endometrial hyperplasia is commonly a consequence of unopposed prolonged estrogen stimulation; some hyperplasias may regress if the estrogenic stimulus is removed and the probability of progression to adenocarcinoma is related to the degree of architectural or cytologic atypia.

CANCER PREVENTION AND SCREENING FOR ENDOMETRIAL CANCER

KEY POINTS

- Formal screening for endometrial cancer is not recommended, even for women taking Tamoxifen.
- All women should be encouraged to promptly report abnormal vaginal bleeding.

Many endometrial cancers may be preventable, particularly those that are estrogen related. Prompt recognition of precursor lesions with the institution of proper treatment is preventive. Because 95% of endometrial carcinomas occur in women 40 years and older, and because endometrial hyperplasia, the precursor state, tends to be a premenopausal and perimenopausal condition, it is appropriate to evaluate individuals past their fourth decade of life if there is abnormal bleeding. Evaluation can be by endometrial biopsy or by dilatation and curettage (D&C) if the biopsy is unsuccessful or the results are unclear. Patients with complex and atypical hyperplasia may be treated by hysterectomy or by periodic use of progestins, depending on age and reproductive desires. Hysterectomy is the preferred treatment in the patient with complex atypical endometrial hyperplasia. This approach not only cures the usual presenting symptoms of abnormal bleeding, but confers prophylaxis against the almost 30% risk of later developing endometrial carcinoma. Since coexistent invasive endometrial cancer may be present in up to 40% of women with CAH, frozen section and surgical staging should be available at the time of hysterectomy.

Those with CAH treated with progestins should have a D&C performed before treatment to rule out the occasional occult carcinoma not detected by biopsy. A progestin should be administered at least 10 to 14 days each month, and endometrial biopsies should be performed at 3- to 4-month intervals to assess treatment results. Women with a uterus should never be prescribed estrogen-only preparations of hormone replacement therapy because unopposed estrogen greatly increases their risk of endometrial cancer. The addition of progestins to the regimens of patients treated with exogenous estrogen may prevent endometrial hyperplasia and subsequent cancer, and may protect against the development of carcinoma.

Women with a uterus who are taking tamoxifen for either treatment or prevention of breast cancer should be informed of the increased risk of endometrial cancer and abnormal vaginal bleeding should be investigated promptly. Obese patients should be counseled that a healthy diet and regular exercise could reduce their risk of endometrial cancer (in addition to other known benefits).

Considering the available knowledge about the disease and available tests, it seems unlikely that screening would be generally advised in the near future. This has also been the view in statements from official organizations like the International Union Against Cancer (UICC) and American

Cancer Society. In spite of lacking evidence-based support, women with a hereditary predisposition to endometrial cancer (i.e., those with HNPCC) should consider screening. The screening of women on tamoxifen therapy with ultrasound or endometrial biopsies is not recommended.

DIAGNOSTIC EVALUATION

KEY POINTS

- All postmenopausal bleeding should be evaluated with office biopsy.
- Endometrioid adenocarcinoma is the most common subtype of epithelial endometrial cancer.
- Serous and clear cell tumors are more likely to have extrauterine spread and preoperative CA-125 and/or imaging is warranted.

Endometrial carcinoma occurs most often in the sixth and seventh decades of life, with an average age at onset of 60 years. It is estimated that 75% of the cases occur in patients 50 years and older, and 95% occur in patients over 40 years of age. The disease, though reported in patients as young as age 16, is rare in patients younger than 30 years of age.

Symptoms of early endometrial carcinoma are few. However, 90% of patients have abnormal vaginal discharge; 80% of these show abnormal bleeding, usually postmenopausal, and 10% show leukorrhea. Other signs and symptoms of more advanced disease include pelvic pressure and other symptoms indicative of uterine enlargement or extrauterine tumor spread.

The standard method of assessing uterine bleeding and diagnosing endometrial carcinoma is the formal fractional D&C. Outpatient procedures, such as endometrial biopsy or aspiration curettage coupled with endocervical sampling, are definitive if positive for cancer. However, if sampling techniques fail to provide sufficient diagnostic information, the fractional D&C is mandatory. Results of endometrial biopsies correlate well with endometrial curettings. However, the methods, individually or combined, may miss an existing endometrial carcinoma and thus patients with atypical hyperplasia treated by less than hysterectomy should be actively followed with endometrial sampling and D&C if results are unclear.

After the diagnosis of endometrial carcinoma has been histologically confirmed, the patient should undergo a thorough evaluation. A complete physical examination and careful medical history can often identify other medical problems that must be evaluated to determine if the patient is a surgical candidate. In general, for well-differentiated endometrioid tumors, an extensive metastatic workup is not necessary. For patients with high-grade tumors, a CA-125 is warranted and imaging studies should be performed if the CA-125 is elevated. Intravenous pyelogram, cystoscopy, and proctoscopy are generally not indicated if the disease is thought to be confined to the uterus.

Diagnostic techniques, such as ultrasonography and magnetic resonance imaging (MRI), are useful in determining myometrial invasion and lymph node involvement in a fairly accurate manner, based on several reports. These techniques however are only applicable when considering conservative treatment of the medically inoperable patient or one desiring future fertility. The only way to accurately diagnose extent and depth of intrauterine invasion is by histologic examination of the hysterectomy specimen.

PATHOLOGY

Hyperplasia

The current classification of endometrial hyperplasia accepted by both the ISGP and the WHO divides hyperplasia on the basis of architectural features into simple or complex and on the basis of cytologic features into typical or atypical. The resulting classification has four categories as follows: simple hyperplasia (SH), complex hyperplasia (CH), simple atypical hyperplasia (SAH), and complex atypical hyperplasia (CAH). The justification for this classification system rests on three retrospective studies that demonstrate a higher rate of progression of CAH to adenocarcinoma.

Progression from hyperplasia to carcinoma occurs in only 1% of patients with SH and in 3% of patients with CH. Progression from atypical hyperplasia is much higher; 8% of patients with SAH and 29% of those with CAH develop carcinoma (Table 8.3).

Pathologic Diagnosis

The ISGP and the WHO last revised the classification of uterine tumors in 1992. This relatively simple classification scheme accommodates the vast majority of endometrial carcinoma, and distinguishes among neoplasms of significantly different prognosis. Mixed carcinomas with two

TABLE 8.3
CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA

Types of Hyperplasia Progressing to Cancer	%
Simple (cystic without atypia)	1
Complex (adenomatous without atypia)	3
Atypical	
Simple (cystic with atypia)	8
Complex (adenomatous with atypia)	29

TABLE 8.4**CORPUS CANCER CLINICAL STAGING, FIGO 1971**

Stage	Characteristics
I	Carcinoma is confined to the corpus
IA	Length of the uterine cavity is 8 cm or less
IB	Length of the uterine cavity is >8 cm
HISTOLOGIC SUBTYPES OF ADENOCARCINOMA	
G1	Highly differentiated adenomatous carcinoma
G2	Differentiated adenomatous carcinoma with partly solid areas
G3	Predominantly solid or entirely undifferentiated carcinoma
II	Carcinoma involves the corpus and cervix
III	Carcinoma extends outside the uterus but not outside the true pelvis
IV	Carcinoma extends outside the true pelvis or involves the bladder or rectum

distinctive cell types are relatively common, and are defined as those carcinomas in which the secondary component constitutes at least 10% of the neoplasm.

The differentiation of a carcinoma is expressed as its grade. Grade 1 lesions are well differentiated and are generally associated with a good prognosis. Both architectural criteria and nuclear grade are used to determine grade. The architectural grade is determined based upon the amount of the tumor growth in solid sheets (Table 8.4). The FIGO rules for grading state that notable nuclear atypia, inappropriate for architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1. Though FIGO did not define notable nuclear atypia, it has been interpreted to include tumors with a majority of cells having nuclei of grade 3, which portends a significantly worse behavior and justifies upgrading by one grade. Some cell types (i.e., serous and clear cell) are not easily architecturally graded because their growth patterns are architecturally limited and in these cases, the nuclear grading is more universally applicable.

Molecular Alterations in the Pathogenesis and Progression of Endometrial Adenocarcinoma

Deletions or mutations of the PTEN gene, and microsatellite instability (MSI) due to hypermethylation of the promoter for the mismatch repair gene, hMLH1, are both relatively common and early events in the development of a significant proportion of endometrioid adenocarcinomas. In contrast, these molecular alterations do not appear critical in

the pathogenesis of serous or clear cell carcinoma (Table 8.2). However, mutations in the p53 gene are found with high frequency not only in invasive serous carcinoma but also in endometrial intraepithelial carcinoma (EIC), the noninvasive precursor of serous carcinoma, suggesting that a different pathway is followed in the development of this second type of endometrial adenocarcinoma. Unpublished data have suggested that MSI may be a good prognostic factor in endometrial cancer. Mutations of the TP53 gene appear to be an early event in the development of serous carcinoma, but a late event in endometrioid carcinomas for which it serves as an indicator of poor prognosis. In addition to the very frequent overexpression of p53 protein in serous carcinoma, it has also been related to high FIGO stage, clear cell histology, higher histologic grade, and increasing depth of myometrial invasion. KRAS, CTNNB1 (β -catenin), PIK3CA, and FGFR2 are also genes commonly mutated in endometrial cancer.

Cell Types

Endometrioid

Endometrioid adenocarcinoma is the most common form of carcinoma of the endometrium, comprising 75% to 80% of the cases. It varies from well-differentiated to undifferentiated. Characteristically, the glands of endometrioid adenocarcinoma are formed of tall columnar cells that share a common apical border. With decreasing differentiation, there is a preponderance of solid growth rather than gland formation.

Foci of squamous differentiation are found in about 25% of endometrial adenocarcinomas. In a GOG study of early-stage disease, it was noted that these tumors with squamous regions behave in a fashion similar to endometrioid carcinomas without squamous differentiation. Historically, the tumors were sometimes separated into adenoacanthoma or adenosquamous carcinoma based on whether the squamous component appeared histologically benign or malignant; however, the terms are confusing, not prognostically relevant, and should be abandoned. Pure squamous carcinoma of the endometrium is extremely rare, representing less than 1% of endometrial carcinoma, and with only about 60 reported cases.

Serous

Serous carcinoma of the endometrium closely resembles serous carcinoma of the ovary and fallopian tube because its papillary growth and cellular features are similar. It is usually found in an advanced stage in older women, when comprehensive surgical staging is performed. Serous carcinoma represents about 10% of endometrial carcinomas, which is fortunate because it is an aggressive tumor. The tumors often deeply invade the myometrium, and unlike typical endometrioid adenocarcinoma, there is a propensity for peritoneal spread. Unfortunately, advanced stage disease or recurrence is common even when serous carcinomas are apparently only minimally invasive, or even confined to the endometrium in polyps.

Since the metastatic disease is often identified only microscopically, about 60% of patients are upstaged following complete surgical staging. A recent report by Wheeler et al. stressed the prognostic importance of meticulous surgical-pathologic staging. They found that serous carcinoma truly confined to the uterus had an overall excellent prognosis, while those with extrauterine disease, even if only microscopic in size, almost always suffered recurrence and death from tumor.

There has been considerable confusion about the definition and significance of papillary carcinoma of the endometrium. A variety of cell types of endometrial adenocarcinoma with differing biologic behavior, including serous, clear-cell, mucinous, and villoglandular carcinoma, may grow in a papillary fashion. Thus, the adjective papillary does not represent a cell type but rather an architectural pattern.

EIC has recently been recognized as a histologically distinctive lesion, which is specifically associated with serous carcinoma of the endometrium. Serous carcinomas most often arise from a background of atrophy or polyps rather than hyperplasia, and are not epidemiologically related to unopposed estrogen stimulation. EIC has been proposed to represent a form of intraepithelial tumor characteristic of serous carcinoma, and it is the likely precursor to invasive serous carcinoma.

Other Cell Types

Clear cell adenocarcinoma of the endometrium is generally recognized and defined on the basis of the distinctive clearing of the cytoplasm of neoplastic cells. About 4% of endometrial adenocarcinomas are of clear cell type. It is a biologically aggressive neoplasm, with a 5-year survival rate varying from only about 20% to 65%.

Mucinous adenocarcinoma is rare in the endometrium, representing approximately 1% of endometrial adenocarcinomas. Mucinous carcinoma of the endometrium has the same prognosis as does common endometrial carcinoma. If an endometrial carcinoma manifests two or more different cell types, each representing at least 10% or more of the tumor, the term mixed cell type is appropriate.

Malignancies in other organs may metastasize to the endometrium. The most common extragenital sites are breast, stomach, colon, pancreas, and kidney, although any disseminated tumor could involve the endometrium. The ovaries are the most likely genital sources of metastasis.

Cancers of an identical cell type may be discovered in the ovary and endometrium simultaneously. Usually, the primary site is assigned to the area having the largest tumor mass and most advanced stage. In certain situations, primary malignancies in the endometrium and ovary may coexist. This "field effect" of the "extended müllerian system" may occur in 15% to 20% of endometrioid carcinomas of the ovary. In a review of a GOG study of 74 patients with simultaneously detected endometrial and ovarian carcinoma with disease grossly limited to the pelvis, only 16% of women suffered a recurrence of disease, with a median follow-up of 80 months. This group of patients was atypical, with 86% having endometrioid histology in both sites.

PATHOLOGIC FACTORS OF PROGNOSTIC SIGNIFICANCE

The importance of uterine and extrauterine risk factors is determined by how they affect the probability of retroperitoneal lymph node involvement and subsequent survival.

FIGO Stage

The prognostic utility of surgico-pathologic stage has been confirmed in multiple studies of large numbers of patients, using both univariate and multivariate analyses. FIGO stage is often the single strongest predictor of outcome for women with endometrial adenocarcinoma in studies using multivariate analyses. Although the FIGO clinical staging system of 1971 was generally useful, retrospective comparison of the two methods demonstrated the clear superiority of surgico-pathologic staging over clinical staging in predicting outcome (Tables 8.4 and 8.5).

Histologic Cell Types

The histologic classification of endometrial adenocarcinoma is important because it has consistently been recognized as an important predictor of biologic behavior and probability of survival. Endometrioid adenocarcinoma accounts for the majority of tumors in the corpus and fortunately usually has a relatively good prognosis.

Adenocarcinoma with squamous differentiation is similar to typical endometrioid adenocarcinoma, with respect to the distribution by age and frequency of nodal metastasis, but is associated with a slightly increased probability of survival. Villoglandular carcinomas have a biologic behavior similar to that of endometrioid adenocarcinoma. Serous carcinoma is an aggressive tumor, with overall survival rates varying from 40% to 60% at five years. Clear cell carcinoma is also a highly aggressive tumor, with 5-year survival rates of 30% to 75%.

Grade

The degree of histologic differentiation has long been considered one of the most sensitive indicators of tumor spread. The GOG and other studies have confirmed that as grade becomes less differentiated, there is a greater tendency for deep myometrial invasion (Table 8.6) and, subsequently, higher rates of pelvic and paraaortic lymph node involvement (Tables 8.7 and 8.8). In fact, 50% of grade 3 lesions have greater than one-half myometrial invasion, with pelvic and paraaortic lymph node involvement approaching 30% and 20%, respectively. Survival has also been consistently related to histologic grade, and in a GOG study of more than 600 women with clinical stage I or occult stage II endometrioid adenocarcinoma, the 5-year relative survival was as follows: grade 1—94%; grade 2—84%; grade 3—72%.

TABLE 8.5**CORPUS CANCER SURGICAL STAGING, FIGO 1988**

Stages/Grades	Characteristics
IA/G123	Tumor limited to endometrium
IB/G123	Invasion to less than half of the myometrium
IC/G123	Invasion to less than half of the myometrium
IIA/G123	Endocervical glandular involvement only
IIB/G123	Cervical stromal invasion
IIIA/G123	Tumor invades serosa or adnexae or positive peritoneal cytology
IIIB/G123	Vaginal metastases
IIIC/G123	Metastases to pelvic or paraaortic lymph nodes
IVA/G123	Tumor invades bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph node
HISTOPATHOLOGY, DEGREE OF DIFFERENTIATION	
Cases should be grouped by the degree of differentiation of the adenocarcinoma:	
G1	5% or less of a nonsquamous or nonmorular solid growth pattern
G2	6% to 50% of a nonsquamous or nonmorular solid growth pattern
G3	More than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on pathologic grading

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1.

In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous-cell carcinomas, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules related to staging

Because corpus cancer is now surgically staged, procedures previously used for determination of stages are no longer applicable, such as the finding of fractional D&C to differentiate between stages I and II.

It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.

Ideally, width of the myometrium should be measured, along with the width of tumor invasion.

TABLE 8.6**HISTOLOGIC GRADE AND DEPTH OF INVASION**

Depth	Grade, No. of Patients (%)			
	G1 (%)	G2 (%)	G3 (%)	Total (% of Total)
Endometrium only	44 (24)	31 (11)	11 (7)	86 (14)
Superficial	96 (53)	131 (45)	54 (35)	281 (45)
Middle	22 (12)	69 (24)	24 (16)	115 (19)
Deep	18 (10)	57 (20)	64 (42)	139 (22)
Total	180 (100)	288 (100)	153 (100)	621 (100)

Source: Reprinted from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. *Cancer*. 1987;60:2035.

TABLE 8.7**GRADE, DEPTH OF INVASION, AND PELVIC NODE METASTASIS**

Depth of Invasion	Grade		
	G1 (N = 180)	G2 (N = 288)	G3 (N = 153)
Endometrium only (N = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (N = 281)	3 (3%)	7 (5%)	5 (9%)
Middle (N = 115)	0 (0%)	6 (9%)	1 (4%)
Deep (N = 139)	2 (11%)	11 (19%)	22 (34%)

Source: From Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. *Cancer*. 1987;60:2039, with permission.

Myometrial Invasion

The depth of myometrial invasion should be recorded in all pathology reports, preferably in both millimeters and in the percentage of total myometrial thickness. Extension of tumor into adenomyosis is not regarded as invasion. Deep myometrial invasion is one of the more important factors

TABLE 8.8

GRADE, DEPTH OF INVASION, AND AORTIC NODE METASTASIS

Depth of Invasion	Grade		
	G1 (N = 180)	G2 (N = 288)	G3 (N = 153)
Endometrium only (N = 86)	0 (0%)	1 (3%)	0 (0%)
Inner (N = 281)	1 (1%)	5 (4%)	2 (4%)
Middle (N = 115)	1 (5%)	0 (0%)	0 (0%)
Deep (N = 139)	1 (6%)	8 (14%)	15 (23%)

Source: From Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: A Gynecologic Oncology Group study. *Cancer*. 1987;60:2039, with permission.

correlated with a diminished probability of survival, and is associated with a higher probability of extrauterine tumor spread, treatment failure, and recurrence. In a GOG study of over 400 women with clinical stage I and occult stage II endometrioid adenocarcinoma, the 5-year relative survival was 94% when tumor was confined to the endometrium, 91% when tumor involved the inner third of the myometrium, 84% when the tumor extended into the middle third, and 59% when the tumor invaded into the outer third of the myometrium. Although the depth of invasion is often inversely related to the degree of differentiation, myometrial invasion is an independent predictor of outcome for women with early-stage endometrial carcinoma.

Vascular Space Invasion

Multiple studies have documented that lymphatic invasion is a strong predictor of tumor recurrence and death from tumor, independent of depth of myometrial invasion or histologic differentiation. Zaino et al. found that vascular invasion was a statistically significant indicator of death from tumor in early clinical stage but not early surgical stage endometrial adenocarcinoma. This suggests that lymphatic invasion helps to identify patients likely to have spread to lymph nodes or distant sites, but that its importance is diminished for those in whom thorough sampling of nodes has failed to identify metastasis. Capillary invasion is identified in 35% to 95% of serous carcinomas of the endometrium, where it has generally been associated with an elevated risk of tumor recurrence or death from disease. Vascular space invasion or capillary-like space involvement with tumor exists in approximately 15% of uteri containing adenocarcinoma. Nodal metastases are more common when capillary invasion is identified.

Adnexal Involvement

Six percent of clinical stage I and occult stage II patients have spread of tumor to the adnexa. Of these, 32% have pelvic node metastases, compared with 8% pelvic node positivity if adnexal involvement is not present. Twenty percent have positive paraaortic node metastases, which is four times greater than if adnexal metastases are not present. Gross intraperitoneal spread without adnexal metastases correlates highly with the involvement of pelvic and paraaortic lymph nodes.

Peritoneal Cytology

About 12% to 15% of patients who undergo surgical staging have positive peritoneal cytology. Of these, 25% have metastases to pelvic lymph nodes, and 19% have metastases to paraaortic lymph nodes. In addition, 35% of patients with extrauterine disease (adnexal, nodal, or intraperitoneal spread) have positive cytologic washings. However, 4% to 6% of patients with positive washings have no evidence of extrauterine disease. Published opinions are mixed about the significance of this finding. Several small series show no outcome differences. However, two large series show peritoneal cytology to be, by itself, a poor prognostic factor. Nonetheless, in 2009 FIGO removed peritoneal washings as a formal component of endometrial cancer staging and suggest that positive cytology should be reported separately but does not affect stage.

Pelvic and Paraaortic Lymph Nodes

In the 1987 GOG study of 621 clinical stage I and occult stage II patients, 70 (11%) had metastases to pelvic or paraaortic lymph nodes. Of this number, 22 patients had metastases to both the pelvic and paraaortic regions, and 12 had metastases to the paraaortic nodes only. The highest rate of paraaortic node metastases (32%) occurred if pelvic nodes were involved. The frequency of pelvic and paraaortic nodal metastases with respect to depth of invasion and grade is shown in Tables 8.7 and 8.8.

PREDICTING NODAL DISEASE

Based on pathologic information available at the time surgery, the risk for nodal metastasis may be estimated. Physicians who selectively perform nodal dissections frequently do so based on the presence of uterine risk factors, which suggest the potential for nodal disease. In patients who did not undergo a nodal dissection at the time of hysterectomy, decisions to offer radiation therapy are commonly based on the estimation of risk for nodal disease based on uterine risk factors. In the surgical pathologic study GOG-33, pelvic and paraaortic nodal diseases were more frequent with increasing grade (% pelvic nodal metastases: 3% grade I, 9% grade II,

18% grade 3), depth of invasion (1% endometrium only, 5% inner 1/3, 6% middle 1/3, 25% outer 1/3 myometrial invasion), and lymphovascular space invasion (LVSI) (27% with LVSI, 7% without LVSI) (60). Pelvic and paraaortic nodal metastases were also more common with cervical involvement, when peritoneal cytology was positive, and when extranodal (adnexal, intraperitoneal sites) disease was found.

DETERMINING THE SURGICAL PROCEDURE

KEY POINTS

- Surgical staging is a critical component for the proper diagnosis and management of all endometrial carcinomas.
- International Federation of Gynecology and Obstetrics stage is the most powerful predictor of prognosis.
- Surgical staging is feasible by laparoscopy and its equivalency is under study.

Of all the female pelvic malignancies, endometrial cancer seems to have more advocates for different treatment plans than any other. The standard treatment for this disease has been and remains a hysterectomy. However, through the years, preoperative and postoperative irradiations have had an important role in the management of this disease.

Contemporary management for most patients with endometrial cancer remains surgical and includes, at the minimum, an initial surgical exploration with collection of peritoneal fluid for cytologic evaluation (intraperitoneal cell washings), through inspection of the abdominal and pelvic cavities with biopsy or excision of any extrauterine lesions suspicious for tumor, and total extrafascial hysterectomy with bilateral salpingo-oophorectomy (BSO). Where the tradition has been to perform this surgery abdominally (typically through a vertical midline incision), laparoscopic management has increasingly been integrated into the forefront. The uterus should be particularly observed for tumor breakthrough of the serosal surface. The distal ends of the fallopian tubes are clipped or ligated to prevent possible tumor spill during uterine manipulation. To complete the surgical staging of endometrial cancer, the removal of bilateral pelvic and paraaortic lymph nodes is also required.

In cases with gross omental or intraperitoneal disease spread, cytoreductive surgery with total omentectomy, radical peritoneal stripping, and occasionally, bowel resection, are required. The goal of reducing the residual to no or small volumes akin to what is performed for ovarian cancer is increasingly considered. In cases complicated by medical comorbidity, advanced age, or obesity, or when nodal dissection cannot or will not be performed, total vaginal hysterectomy with or without laparoscopic assistance may also be utilized. Following surgical assessment, patients may be classified based on pathologic features as to their risk of recurrence, and

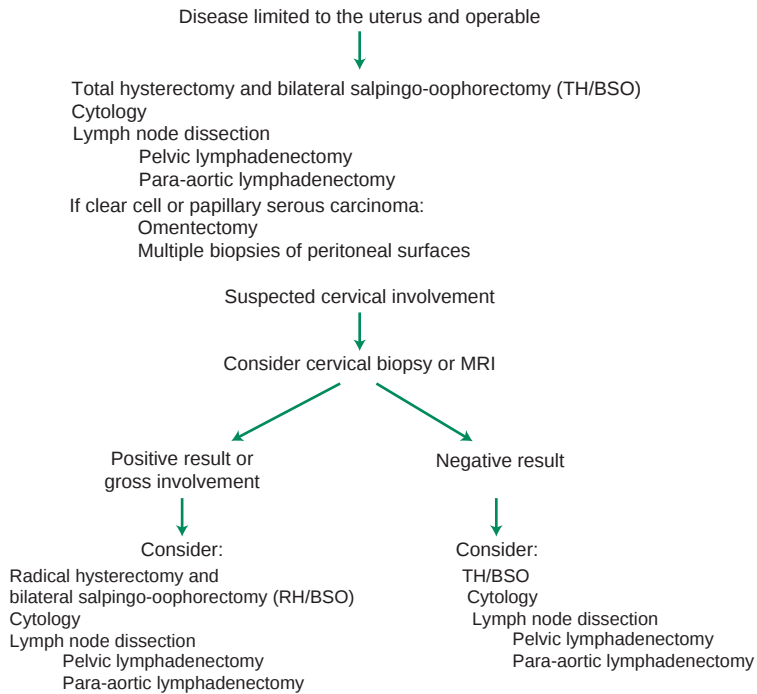


FIGURE 8.1. Surgical management of early-stage endometrial cancer (stages I and II). Patients with stage I and II endometrial cancers are treated with total hysterectomy (TH), BSO, peritoneal cytology, and pelvic and paraaortic lymphadenectomy. Many advocate lymphadenectomy when feasible for all patients with early-stage endometrial cancer regardless of grade or depth of myometrial invasion.

Source: From Markman M, ed. *Atlas of Cancer*. 2nd Ed. Philadelphia, PA: Current Medical Group; 2008.

those deemed to be at sufficient risk may be offered adjuvant therapies. An algorithm for surgical approach can be found in Figure 8.1.

Nonsurgical Management

The management of most patients with endometrial cancer is surgical. The decision to use surgery is a function of patient and disease status. Patients with significant medical comorbidities who are not acceptable candidates for surgery (markedly advanced age, diminished performance status, severe cardiac/pulmonary disease, and massive obesity) may be managed by alternative means. Primary radiation therapy without surgery has been used, and is discussed later in this chapter. Progestational therapy may be used for those who are inoperable or in younger patients who elect for fertility preservation.

Patients who are obese but otherwise surgical candidates may undergo an abdominal panniculectomy to enhance surgical exposure to facilitate hysterectomy and nodal dissection. Approximately 5% of women with endometrial cancer are diagnosed under the age of 40. For some younger women, the standard treatment of hysterectomy is unacceptable due to desires to maintain fertility. Patients without myometrial invasion are thought to be the best candidates, and may undergo pelvic MRI to assess for myometrial involvement. Progestational therapy, delivered orally or intrauterinely, has been successful in reversing malignant changes in up to 76% of cases. Because response may be temporary or incomplete, periodic sampling of the endometrium is advised.

Nodal Dissection

The value of staging any malignancy relates to the ability to describe the extent of disease at diagnosis and to define comparable patient populations for whom prognosis and therapy are similar. The value of surgical staging as it relates to endometrial cancers is a source of controversy and has been the subject of increased scrutiny and debate over the last several years. Proponents of routine surgical staging suggest that the ability to identify otherwise unrecognized disease spread to the nodes changes the postoperative therapies that are given, and is the most accurate way to assess risk. Most controversial is the assertion that surgical staging has a therapeutic benefit independent of the node status (positive or negative for metastatic disease).

Fundamentally, surgeons must determine for themselves whether or not surgical staging has sufficient value to offer it to all patients or only to those selected based on risk factors identified preoperatively and intraoperatively. The principal risks attributable to nodal dissections include increased operative time, potential for blood loss associated with vascular injury, genitofemoral nerve injury with resulting numbness and paresthesia over medial thighs, lymphocyst formation, and lymphedema. In general, the risks associated with nodal dissections are low and acceptable. The principal advantage of comprehensive staging is that the physician and patient are provided with the greatest amount of information. In the contemporary management of endometrial cancer, this information results in less use of radiation, and substitution of vaginal cuff brachytherapy for pelvic radiation.

The importance, extent, and technique of nodal dissection are hotly debated. Questions relate to which patients should be offered and could benefit from surgical staging (all, some, or none), and what is the optimal surgical procedure to be performed (biopsy of enlarged/visible nodes, lymphadenectomy). Controversy also exists between those surgeons who perform only pelvic dissections and those who advocate pelvic and paraaortic nodal dissection.

Nodal Dissection—None

Most patients with endometrial cancer do present with low-risk features. In the entire GOG-33 study population of 621 patients, 75% had grade 1

to 2 tumors, and 59% had inner 1/3 or less myometrial invasion. Only 9% of patients had positive lymph nodes. The Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) trial evaluated patients with stage IC, grade 1; stages IB and IC, grade 2; or stage IB, grade 3 who underwent hysterectomy without lymph node dissection and compared observation to postoperative pelvic radiation. This patient population managed without nodal dissection and had favorable outcomes with or without radiation therapy (5-year survival rates of 85% observation, 81% with pelvic radiation) in the PORTEC study.

The only randomized trial comparing lymphadenectomy to no nodal assessment has recently been reported. A Study in the Treatment of Endometrial Cancer (ASTECC) randomized patients with endometrial cancer treated with hysterectomy to pelvic lymphadenectomy or not. Following surgery, patients with stage I and IIA diseases were then randomized again to observation or pelvic radiation therapy if they had grade 3, serous, or clear cell histology, more than 50% myometrial invasion, or endocervical glandular invasion (stage IIA). Treatment centers were also permitted to use vaginal cuff brachytherapy regardless of pelvic radiation assignment. The results show no evidence of benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer.

Nodal Dissection—Selective

Increasingly, some form of nodal assessment has been integrated into the upfront management of endometrial cancer, and nodal assessment has been incorporated into the staging of endometrial cancer since 1988. Surgical staging is the most accurate way to determine the extent of disease spread. Palpation of pelvic lymph nodes is not sufficiently accurate.

An assessment of pelvic and paraaortic lymph nodes is required to assign stage according to FIGO 1988. In GOG-33, the rate of paraaortic nodal involvement was roughly 50% of the pelvic node rate. As an isolated finding, paraaortic nodes were involved in only 2% of cases. Intraoperative assessment of the uterus has been used to guide the surgeon as to when to perform a nodal dissection. Gross inspection of the uterus immediately following its removal can be used to estimate the degree of myometrial invasion.

Nodal Dissection—Routine

Many gynecologic oncologists have moved toward performing uniform comprehensive surgical staging for nearly all patients with endometrial cancer. The rationale for uniform staging includes the lack of a patient population for whom nodal disease is so low that nodes should be omitted, the inaccuracy of preoperative or intraoperative assessments predicting the risk for nodal disease, the potential for therapeutic benefit in node positive and negative patients, and the lack of significant morbidity associated with the procedure. Postoperative adjuvant decisions are best made with the most complete information. If nodal assessment is the predominant factor by which to categorize patients into risk groups, routine nodal dissection is the best method by which to determine which few patients will require adjuvant therapy.

Laparoscopic Management

Laparoscopic management of endometrial cancer has increasingly been integrated into standard practice. Laparoscopic techniques are utilized in the initial treatment of endometrial cancer (laparoscopic assisted vaginal hysterectomy, total laparoscopic hysterectomy), to stage patients with laparoscopic pelvic and paraaortic nodal dissection, and to re-stage patients following incomplete surgical staging.

The largest and most comprehensive data set to date comes from the large prospective randomized trial conducted by the GOG (Lap II trial). The study was designed to compare laparoscopic hysterectomy with comprehensive surgical staging to the traditional laparotomy technique (using a 2:1 randomization favoring the laparoscopic arm) to determine the complete staging rates, safety, short term surgical outcomes, and long-term cancer recurrence and survival. The study enrolled 920 patients to the open arm, and 1,696 to laparoscopy. The rate of conversion from laparoscopy to open procedure was 26%, and was most frequently related to poor visibility (15%), extrauterine cancer spread (4%), and bleeding (3%). The conversion rate increased with an increasing patient obesity, with laparoscopic success rate being 90% with a BMI < 20, 65% with BMI = 35, and 34% with BMI = 50. Median number of removed nodes was similar between each technique, as were the frequencies of patients found to have positive lymph nodes. Complication rates (combined rates of vascular, urinary, bowel, nerve, or other complications) for those who had an open procedure were 7.6%, compared to 9.5% of patients randomized to laparoscopy. Of the 1,242 patients randomized to laparoscopy who had the procedure successfully completed laparoscopically, the complication rates were 4.9%. Comparing patients who underwent open surgery versus successful completion of laparoscopy, operative time was longer (median, 70 min), but hospital time was shorter (2 vs. 4 days) with laparoscopy. Long-term recurrence and survival data are maturing. The authors concluded that laparoscopic surgical staging is an acceptable, and possibly better option, particularly when the surgery can be successfully completed laparoscopically.

Laparoscopic surgery has demonstrated an important role in the management of endometrial cancer. The demonstration of comparable surgical endpoints (similar numbers of nodes removed, similar frequency of positive nodes) along with shortened hospital stay and quicker recovery compared to open procedures suggests that appropriate patients should be counseled regarding this option. Long-term follow-up demonstrating equivalent recurrence rates and survival are also required.

Surgical Recommendations

The contemporary management of endometrial cancer has significantly changed. The indications for nodal dissections are rapidly evolving and presently subject to controversy. Patients who *a priori* are deemed not to be candidates for staging should be considered for vaginal or laparoscopic-assisted vaginal hysterectomies. As randomized trials mature, surgical treatment will likely be individualized to the risk of lymph node metastases. Comprehensive staging most accurately assigns stage and associated prognosis.

Staging also allows for a more tailored approach to the use of adjuvant therapies. Laparoscopic techniques have been shown to result in comparable surgery to open procedures. For patients with resectable intraperitoneal disease, cytoreductive surgery may improve outcomes.

Postoperative Surveillance

KEY POINTS

- Routine physical examination in combination with prompt reporting of symptoms is probably the best method for detecting recurrent disease.
- Pap smears detect only a small fraction of recurrent disease.

The frequency and extent of follow-up visits and surveillance tests for patients with a history of gynecologic cancer have traditionally been based on arbitrary guidelines that have been established and perpetuated at various institutions throughout the United States. Since the majority of patients with endometrial cancer will do well, and there is no clear evidence that early detection of disease recurrence will improve outcome, it has become necessary to re-evaluate the practice of routine intensive surveillance in women with a history of endometrial cancer.

Physicians should educate patients regarding the signs and symptoms of recurrent disease and act promptly to evaluate symptomatic patients with diagnostic tests targeted toward the symptoms. Obtaining Pap smears routinely at each follow-up visit does not appear to be beneficial. Elevated levels of the tumor-associated antigen CA-125 have been documented in patients with advanced/recurrent endometrial cancer; however, the value of surveillance CA-125 levels is limited and best reserved for patients with an elevated value at initial diagnosis. Based on the knowledge that the majority of recurrences occur within the first 3 years after surgery, it is recommended that patients undergo semi-annual pelvic examinations for 3 years, then annually thereafter. There is no evidence in the literature that routine chest X-rays improve survival, and Pap smears do not improve the outcome of patients with isolated vaginal recurrences. Low-risk women may be able to be followed less frequently to allow more detailed investigation of the high-risk women.

GENERAL MANAGEMENT

KEY POINTS

- Adjuvant radiation for early-stage disease can reduce local recurrence with no appreciable effect on overall survival.
- Intravaginal radiation therapy is probably sufficient for comprehensively staged patients with early-stage disease.
- Chemotherapy is preferable to whole abdominal radiation in advanced stage disease.
- Combination therapy is currently being studied in advanced stage disease.

Early uncontrolled trials suggested that progestin therapy after surgery or irradiation was associated with a decreased risk of recurrence in patients with disease confined to the uterus. However, large prospective randomized trials failed to confirm a survival advantage. Radiation therapy has been and remains the standard adjuvant treatment modality for most patients at risk for recurrence. This standard continues to evolve however.

Two prospective trials comparing radiation therapy to chemotherapy has since shown similar outcomes for patients treated with chemotherapy or radiation therapy. Adjuvant chemotherapy improved progression-free survival (PFS) and survival in patients with advanced stage disease compared to whole abdominal radiotherapy suggesting an important role for first-line therapy that includes chemotherapy. Current research focuses on whether outcomes may be improved by adding chemotherapy either sequentially or concomitantly with radiation.

Adjuvant Treatment

A postoperative treatment plan should take into account the prognostic factors determined by the surgical-pathologic staging. Patients can be classified into three categories: those who show a high rate of cure without postoperative therapy, those who yield a low rate of cure without postoperative therapy, and those who demonstrate a reduced rate of surgical cure and may benefit from additional therapy. The postoperative treatment plan should also consider the available postoperative treatment methods and their morbidities. Chemotherapy as adjuvant treatment for patients with stage III and IV endometrial carcinomas is recently supported by data from GOG-122 and is discussed separately. Adjuvant radiation therapy is continually evolving and currently intravaginal brachytherapy and external beam whole pelvic therapy with or without an extended field are commonly employed (Table 8.9).

ADJUVANT RADIATION THERAPY

Radiation therapy plays a significant role in the management of endometrial cancer. It is often used as an adjuvant treatment after surgery, or as definitive treatment for patients who are medically inoperable, or with local recurrence. In the past, most patients were treated with preoperative intracavitary brachytherapy with or without external beam radiotherapy followed by hysterectomy. This approach is not without merit, especially in patients with gross cervical involvement. However, most patients nowadays undergo surgery first; then, depending on the prognostic features obtained from the pathology review, the need for radiotherapy is determined.

Early-Stage Disease

Most of the data on adjuvant radiation in endometrial cancer pertain to patients with early-stage (I and II) disease. The role of radiation in this group of patients, however, has been undergoing significant scrutiny is the

TABLE 8.9**TREATMENT RECOMMENDATIONS AT MSKCC
FOR SURGICALLY STAGED I AND II PATIENTS**

Stage	Grade		
	1	2	3
IA	Observation	Observation	IVRT or observation ^a
IB	IVRT or observation ^a	IVRT or observation ^a	IVRT
IC	IVRT	IVRT	IVRT or IMRT ^b
IIA	IVRT	IVRT	IVRT
IIB < 50% CSI	IVRT	IVRT	IVRT
IIB > 50% CSI	IMRT	IMRT	IMRT

^aObservation is offered to patients less than 60 years old and without lympho-vascular invasion (LVI).

^bIMRT if outer third invasion and/or positive LVI.

CSI, cervical stromal invasion; IVRT, intravaginal radiotherapy; IMRT, intensity modulated radiotherapy.

last 5 years. Most of the debate focuses on the benefit of adjuvant radiation and to a lesser extent the type of radiation that needs to be used.

The Benefit of Adjuvant Radiation

Two recent prospective randomized trials compared surgery alone to surgery and postoperative external beam radiation. The first trial was conducted by GOG 99 where 390 patients with stage IB and IIB endometrial cancers who underwent TAH/BSO and pelvic/para-aortic lymph nodes sampling were randomized to observation ($n = 202$) or postoperative pelvic radiation ($n = 190$). With a median follow-up of 69 months, the 4-year survival rate was 92% in the irradiation arm, compared with 86% in the observation arm ($p = 0.6$). The 2-year estimated PFS rate was 97% versus 88% in favor of the irradiation arm ($p = 0.007$), with the greatest decrease seen in vaginal/pelvic recurrences. The second trial was the PORTEC where 714 patients with stage IB grades 2, 3 and stage IC grades 1, 2 were randomized after TAH/BSO and NO lymph nodes sampling to observation ($n = 360$) or pelvic radiation ($n = 354$). With a median follow-up of 52 months, the 5-year vaginal/pelvic recurrence rate was 4% in the radiation arm compared to 14% in the observation arm ($p < 0.001$). The corresponding 5-year survival rates were 81% and 85%, respectively ($p = 0.37$).

Despite the fact that adjuvant radiation significantly improved local-regional control, most of the debate focuses on the lack of improvement in overall survival. Because of relatively high incidence of other comorbidities, the chance of dying from an intercurrent illness is as high if not higher than dying from endometrial cancer. As well, many of the patients who develop local recurrence after surgery alone are often salvaged with subsequent radiation. Even in patients who die from endometrial cancer, the most common cause is distant rather than local relapse. In the PORTEC trial, the 8-year mortality rates from local versus distant relapse were 1.1% and 7.9%, respectively, in the RT group and 2% and 5.2% in the surgery alone group. It is unrealistic to expect a local treatment modality, such as radiation, to alter this pattern of relapse.

The Type of Radiation

There are two types of radiation (intravaginal brachytherapy or external beam radiation) that could be used either alone or in combination for early-stage endometrial cancer.

A significant reduction in local recurrence rates has been seen with the addition of pelvic radiation to intravaginal brachytherapy (1.9% vs. 6.9%, $p < 0.01$). With regard to overall survival, there was no significant difference between the two treatments but in the subset of patients with grade 3 disease and deep myometrial penetration there was a survival advantage (cause-specific survival) of 18% versus 7% in favor of the pelvic radiation arm.

Pelvic radiation alone or combined with intravaginal brachytherapy has been studied. The corresponding 5-year pelvic control and disease-free survival rates were 96% versus 93% ($p = 0.32$) and 88% versus 83% ($p = 0.41$). This study as well as others called into question whether the addition of vaginal radiation is needed.

With the increase in surgical lymph node staging, the use of postoperative intravaginal brachytherapy alone regained its appeal. The rationale was that full surgical lymph node staging could potentially eliminate the need for pelvic radiation while vaginal brachytherapy could still address the risk of vaginal cuff recurrence. Several reports in the past 5 years showed indeed a very low rate of recurrence either in the vagina or the pelvis with such an approach.

From the above discussion, it is clear that the options available for patients with early-stage endometrioid endometrial cancer are numerous. Perhaps it is better to consider different options based on following factors: stage and grade, whether surgical lymph nodes staging was done, and the risk of nodal versus vaginal recurrence. The therapeutic ratio of adjuvant external beam radiation is very likely to benefit from the advances in IMRT (intensity modulated radiation therapy) by providing the most conformal dose distribution to the tumor volume while sparing the surrounding normal structures.

Surgically Staged Patients

A reasonable alternative to observation in patients who had surgical lymph node staging is intravaginal brachytherapy alone. Horowitz et al. reported on 81 patients with IB grade 3-IC who were treated with surgery including lymph nodes dissection followed by high-dose rate intravaginal brachytherapy. Of the 81 patients, only 2 (2.4%) had vaginal recurrence and only 1 (1%) had pelvic recurrence.

No Surgical Lymph Node Staging

In those patients with stage IB grade 3-IC without surgical lymph node staging, intravaginal brachytherapy alone does not seem to be adequate. Pelvic radiation alone is sufficient without the addition of intravaginal radiation. In patients without comprehensive surgical staging, completion lymphadenectomy is also a reasonable consideration in an attempt to minimize the delivery of unnecessary whole pelvic radiation.

Advanced-Stage Disease

Radiation

The outcome of patients with isolated adnexal involvement (stage IIIA) treated with pelvic radiation is reasonably good. Patients with isolated serosal involvement (stage IIIA) do worse than those with isolated adnexal involvement. Patients with stage IIIC disease, by virtue of paraaortic node involvement, represent a particularly high-risk group. Following surgery, these patients are generally treated with extended field radiation to encompass the pelvis and the paraaortic regions.

Chemoradiation

In the GOG-122 trial, there were 396 patients with stage III and optimally debulked stage IV disease who were randomized to whole abdomen radiation ($n = 202$) or to doxorubicin-cisplatin chemotherapy ($n = 194$). With a median follow-up of 74 months, there was significant improvement in both PFS (50% vs. 38%; $p = 0.007$) as well as overall survival (55% vs. 42%; $p = 0.004$), respectively, in favor of chemotherapy. Another randomized trial comparing adjuvant radiation to chemotherapy (doxorubicin-cisplatin-cyclophosphamide) in patients with stage I to III (2/3rd stage III) was recently reported and showed no difference in outcome between the two arms. With a median follow-up of 95.5 months, the 5-year disease-free survival was 63% in both arms ($p = 0.44$) and the 5-year overall survival rate was 69% in the radiation arm compared to 66% in the chemotherapy arm ($p = 0.77$). What those two trials show is that chemotherapy at a minimum is equivalent to radiation in this group of patients and ought to be used, not alone but in combination with radiation.

SPECIAL SITUATIONS

Serous and Clear Cell Histologies

Serous cancer and, to a lesser extent, clear cell cancer tend to spread in a fashion similar to ovarian cancer with a high propensity for upper abdominal relapse. Therefore, whole abdomen radiation and chemotherapy have both been studied in this group of patients. Patients with early-stage disease who are surgically staged can be treated with intravaginal radiation given with carboplatin/taxol chemotherapy while those with advanced-stage are given tumor-directed radiation and/or chemotherapy.

Definitive Radiation for Inoperable Disease

Patients with medically inoperable stage I to II uterine cancers are usually treated in a fashion similar to those with cervical cancer by using intracavitary applicators with or without pelvic radiation. For patients with clinical stage I grade 1 or 2 and no evidence of myometrial invasion or lymph node metastasis on MRI, intracavitary brachytherapy alone is sufficient. More recently, high-dose-rate brachytherapy is also being employed.

COMPLICATIONS OF RADIATION

Pelvic Radiation

In the PORTEC randomized trial, the overall (grades 1 to 4) rate of late complications was 26% in the RT group compared to 4% in the observation group ($p < 0.0001$). Most of the late complications in the RT group, however, were grades 1 and 2 (22%) and only 3% were grades 3 and 4. It is also important to note that many patients in this trial were treated with AP/PA fields where the overall rate of complications was 30% compared to 21% for those treated with 4-field box ($p = 0.06$).

Whole Abdomen Radiation

The toxicity is more pronounced than pelvic radiation but not as high as expected. In GOG-94, the grade 4 gastrointestinal toxicity was seen in six patients (3.8%). Severe liver toxicity was seen in 3 out of 158 evaluable patients (2%), with 2/3 recovering without sequelae. There were no grade 3 and 4 genitourinary toxicities.

Intravaginal Brachytherapy

The main advantage of this treatment is its ability to deliver a relatively high dose of radiation to the vagina while limiting the dose to the surrounding normal structures such as bowels and bladder. This advantage is manifested with the low rate of severe late toxicity seen with this treatment technique ranging from 0% to 1%. But such a low rate of severe complications cannot be taken for granted because special attention needs to be paid to the depth of prescription, dose per fraction, the length of vagina treated, and the diameter of the cylinder used.

Radiation therapy can be curative in a select group of patients with small vaginal recurrences who have not received prior radiation. The 5-year local control rate ranges from 42% to 65% and the 5-year overall survival rate from 31% to 53%.

TREATMENT OF RECURRENT DISEASE

KEY POINTS

- Radiation therapy is useful for local recurrences in patients who have not been irradiated previously.
- Surgery is an excellent option for isolated disease that can be completely resected.
- Hormonal therapy is often active in patients with well-differentiated tumors.
- Multiagent chemotherapy is more active than single agents and the optimal combination is under active investigation.

Patients with recurrent endometrial cancer must be fully evaluated for sites of recurrent disease. Depending on the site of the recurrence and prior therapy, patients may be treated for palliation or for cure. Treatment may consist of irradiation, surgery, endocrine therapy, or cytotoxic chemotherapy. These agents may be used singly or in combination. It is uncommon for patients with recurrent disease to be cured unless the recurrence is only in the vaginal cuff or central pelvis. Therefore, close follow-up after primary therapy with pelvic exams and Pap smears is important.

SYSTEMIC THERAPIES

Endocrine Therapy

Hormonal agents have been found to be valuable, particularly in the patient with recurrent disease, and reviews of their use have been extensively published. Response rates to a variety of endocrine agents including

TABLE 8.10**RESPONSE TO ENDOCRINE THERAPY**

Hormonal Agent	Average Dose	Response Rate (%)	Range (%)
Hydroxyprogesterone caproate (Delalutin)	1–3 g IM q week	29	9–34
Medroxyprogesterone acetate (Provera)	200–1,000 mg IM q week or po qd	22	14–53
Megestrol acetate (Megace)	40–800 mg po qd	20	11–56
Tamoxifen (Nolvadex)	20–40 mg po qd	10	0–53
Goserelin acetate	3.6 mg SC q month	11	NA
Anastrozole (SERM)	1 mg po qd	9	NA
Arzoxifene (SERM)	20 mg po qd	31	NA

NA, not applicable; SERM, selective estrogen receptor modulator.

progestins, antiestrogens, and aromatase inhibitors are presented in Table 8.10. The overall response to progestins is approximately 25%. A higher dose of progestin does not appear to increase the response rate. Tamoxifen has been investigated in patients with recurrent disease in several studies. Results have varied, but in general, response rates have been modest in untreated patients. The possibility of alternating tamoxifen with megestrol acetate in order to exploit the recruitment of progesterone receptors by tamoxifen has also been tested with some success by the GOG.

Cytotoxic Chemotherapy

Both single-agent and combination regimens are capable of inducing objective responses, yet the median time to treatment failure is on average 3 to 6 months and the overall survival of patients with metastatic endometrial cancer is generally less than 12 months. The role of chemotherapy in the recurrent disease setting remains palliative, and minimizing side effects is of equal importance when selecting a regimen.

Single-Agent Trials

A wide variety of single agents has been tested. Despite the number of drugs evaluated, the most commonly used single agents today based on response rates of at least 20% include cisplatin, carboplatin, doxorubicin, epirubicin, ifosfamide, docetaxel and paclitaxel, and more recently topotecan has been added to this list. Frequent variability in response rate has been noted for the same agent and is probably related to several factors, including prior treatment, performance status, extent of disease, and the response criteria used for evaluation. No current data suggest that dose-response relationships exist for single-agent therapy, and doses and schedules are generally adjusted to minimize toxicity for an individual patient.

Combination Therapy

The results of treatment with combination regimens are presented in Table 8.11. The results of GOG-107 comparing doxorubicin (60 mg/m² every 3 weeks) with the same doxorubicin dose and cisplatin (50 mg/m² every 3 weeks) in 223 patients with advanced or recurrent endometrial cancer have shown a significantly higher response rate for the combination (42% vs. 25%, $p = 0.004$), but a PFS and overall survival of 5.7 versus 3.8 months and 9.2 versus 9.0 months, respectively. This study confirms a higher response rate with combination therapy, but the difference in PFS is modest and likely not clinically meaningful; the overall survival is identical in the two groups.

The disadvantage of GOG-163 was the lack of platinum in the taxane-containing arm, however. The addition of a taxane which was subsequently studied in GOG-177 evaluating doxorubicin (60 or 45 mg/m² in patients with prior radiotherapy) with cisplatin (50 mg/m²) as the standard arm versus paclitaxel (160 mg/m²) with doxorubicin (45 mg/m²) and cisplatin (50 mg/m²) and G-CSF as the investigational regimen.

Overall, TAP chemotherapy increased 12-month survival to 59% compared to 50% with AP with an HR of 0.75 (0.56 to 0.998). Although the TAP regimen produced an improvement in response rate and PFS, survival was minimally increased, and it is associated with greater toxicity. The combination of paclitaxel and carboplatin as a doublet has also been evaluated in a variety of Phase II trials and retrospective studies with response rates in the 43% to 80% range. No direct Phase III comparisons between doxorubicin and platinum versus paclitaxel with platinum are currently available. GOG-209 comparing doxorubicin, cisplatin, and paclitaxel with cisplatin and paclitaxel has recently completed accrual and will provide an important comparison of efficacy and toxicity between these two regimens when the data mature.

Investigational Agents

A variety of investigational agents have been proposed as appropriate for evaluation in patients with endometrial cancer. These agents have generally failed to demonstrate sufficient activities for further development.

TABLE 8.11

RANDOMIZED TRIALS OF COMBINATION CHEMOTHERAPY*

GOG trial #	Drug	Dose (mg/m ²)	n	CR/PR
48	DOX	60	132	5%/17%
	<i>vs.</i>			
	CYC	500	144	13%/17%
107	DOX	60	150	8%/17%
	<i>vs.</i>			
	DOX	60	131	19%/23%
163	CIS	50		
	<i>vs.</i>			
	DOX	50	157	15%/25%
177	PAC	150	160	17%/26%
	<i>vs.</i>			
	DOX	60	129	7%/27%
	CIS	50		
	<i>vs.</i>			
	DOX	45	134	22%/35%
	CIS	50		
	PAC	160		

CYS, cyclophosphamide; DOX, doxorubicin; CIS, cisplatin; PAC, paclitaxel, CR, complete response; PR, partial response.

*All trials are were conducted in chemo-naïve patients and each regimen is given on a q3week schedule

More recently, as in other tumor types, agents targeting specific molecular pathways are in various early stages of evaluation.

SEROUS AND CLEAR CELL HISTOLOGIES CHEMOTHERAPY

Serous cancer and to a lesser extent clear cell cancer tend to spread in a fashion similar to ovarian cancer, with a high propensity for upper abdominal relapse. With whole abdomen RT, the rate of relapse is still substantial, indicating the need for effective systemic therapy. Based on the response rates of paclitaxel and carboplatin in other tumors of serous histology, trials investigating paclitaxel and carboplatin in uterine papillary serous

carcinomas (UPSCs) have reported response rates of 60% to 70%. Recognizing the limits of retrospective studies, data support the potential benefit of a regimen of platinum-based chemotherapy with cuff irradiation in patients with UPSC. Randomized prospective data are needed to accurately define the best approach in these patients.

FUTURE DIRECTIONS

In 2001, the National Cancer Institute convened an expert panel to develop a national 5-year plan for research priorities in gynecologic cancers. The resulting report, Priorities of the Gynecologic Cancer Progress Review Group (PRG), specified that understanding tumor biology was the central key toward controlling gynecologic cancers. For endometrial cancer, one of the top research priorities defined by the PRG was to identify prognostic and predictive markers for treatment efficacy and toxicity. One of the key research issues in endometrial cancer relates to developing a more comprehensive and detailed understanding of cancers at a genetic and molecular level. By understanding these factors, a more rationale development of targeted agents is hoped.

SUMMARY

Endometrial cancer is the most common gynecologic malignancy, and an understanding of presentation, surgical management, and treatment options is required for gynecologic oncologists. Surgical therapy is the mainstay of endometrial cancer, with lymphadenectomy and laparoscopy increasingly integrated. A thorough knowledge of the relationships between uterine factors and extrauterine disease spread is essential. Surgical staging defines extent of disease and largely defines risk of recurrence. Radiation is associated with better local control, but with no improvement in survival for patients with stage I and II endometrial cancers in randomized trials.

Chemotherapy is increasingly integrated into upfront management of advanced-stage endometrial cancer, and may have a role in early-stage disease. Combination therapy with radiation and chemotherapy is under evaluation. Targeted agents hold promise; however, a better understanding of molecular and genetic changes is required to improve efficacy.

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CHAPTER 9 ■ THE CORPUS: MESENCHYMAL TUMORS

Uterine sarcomas are rare malignancies accounting for as few as 6% of the estimated 39,080 cases of cancer of the uterine corpus in the United States in 2007. Although the general prognosis of endometrial adenocarcinomas is excellent (a projected 7,470 disease-related deaths in 2008), uterine sarcomas are generally aggressive and overall mortality rates approached 90% in early reports. Uterine sarcomas encompass a broad spectrum of neoplasms from pure parenchymal tumors and endometrial stromal tumors (leiomyosarcomas and endometrial stromal sarcomas) to mixed epithelial/stromal tumors, such as adenosarcoma and carcinosarcoma, and represent from 1% to 3% of all uterine malignancies.

EPIDEMIOLOGY AND RISK FACTORS

KEY POINTS

- Carcinosarcoma patients are older than those with other uterine sarcomas.
- Uterine sarcomas are more common in African-American women.
- Prior radiotherapy is a risk factor for carcinosarcoma.

The two major sarcomas, leiomyosarcoma and carcinosarcoma, are distinguishable in several ways, including clinical presentation, spread patterns, mean age at diagnosis, racial distribution, apparent relative incidence, method of diagnosis, and history of prior radiotherapy. Figure 9.1 demonstrates mean ages at diagnosis for common uterine sarcomas and endometrial adenocarcinomas. Patients with carcinosarcomas are on the average 5 to 10 years older than those with endometrial adenocarcinomas, müllerian adenosarcomas, leiomyosarcomas, and endometrial stromal tumors. Thus, many patients with carcinosarcomas are postmenopausal, whereas those with leiomyosarcomas may be premenopausal or perimenopausal at the time of diagnosis.

Women with carcinosarcomas are more likely to be of African-American descent than those with endometrial adenocarcinomas. The age-adjusted incidence of uterine sarcomas in African-American women is approximately twice that of Caucasian women. Carcinosarcomas and leiomyosarcomas constitute about 4% and 1.5% of all uterine malignancies, respectively. Because the risk profile of carcinosarcomas so closely parallels that of endometrial adenocarcinomas with regard to obesity, diabetes, anovulation, and low parity, it has been suggested that they be regarded as “metaplastic” endometrial carcinomas instead of true sarcomas.

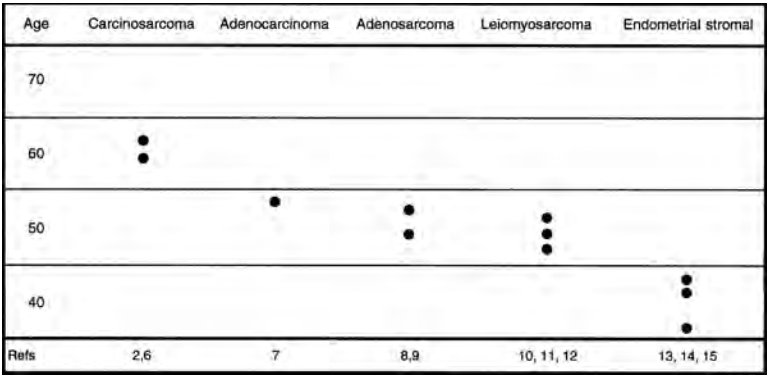


FIGURE 9.1. Mean age at diagnosis of common uterine sarcomas and endometrial adenocarcinomas.

Although as many as a third of patients with carcinosarcomas in some series have a history of antecedent pelvic radiotherapy, this is rarely, if ever, an etiologic factor in patients with leiomyosarcoma of the uterus. It has been suggested that postirradiation carcinosarcomas occur at a younger average age than those arising *de novo*. Carcinosarcomas in previously irradiated patients also tend to present in advanced stage, perhaps because radiotherapy is often associated with cervical stenosis and, thus, no telltale uterine bleeding.

CLINICAL PRESENTATION

Vaginal bleeding is the most common presenting symptom in women with uterine sarcomas in general and is nearly universal in those with carcinosarcomas. Vaginal bleeding occurs in as few as 40% of women with leiomyosarcomas, however. A typical presentation of carcinosarcoma is vaginal bleeding associated with a protuberant, fleshy mass from the cervix. These neoplasms arise in the endometrial lining but often grow in an exophytic pattern within the endometrial cavity (Fig. 9.2).

Uterine enlargement and a presumptive diagnosis of uterine leiomyomata are nearly universal findings in patients with leiomyosarcoma. The incidence of leiomyosarcoma in all patients with the clinical picture of myomas is less than 1% but increases with age to slightly over 1% in the sixth decade of life.

DIAGNOSIS AND EVALUATION

Whereas the diagnosis of carcinosarcoma is confirmed, or at least suggested, at the time of endometrial biopsy or curettage, leiomyosarcomas are rarely diagnosed before hysterectomy. Although positron-emission tomography



FIGURE 9.2. Exophytic pattern of growth in carcinosarcoma.

and magnetic resonance offer the potential of differentiating between benign and malignant smooth muscle tumors of the uterus, these techniques are not sufficiently sensitive and specific at the present time (Fig. 9.3).

Patients with uterine carcinosarcomas much like high-grade endometrial lesions, unless presenting with clinical metastases, should be managed in referral centers where appropriate surgical staging can be performed. The utility of chest tomography in uterine sarcomas has not been formally addressed but should be considered in patients with high-grade lesions. Since no specific data are in place for uterine sarcomas, CT scanning may be indicated in patients with high-grade sarcomas to determine the extent of surgery.

STAGING AND NODAL INVOLVEMENT

By convention, the 1988 International Federation of Obstetrics and Gynecology staging criteria for endometrial cancer are used to assign stages in uterine sarcomas. Carcinosarcomas, like endometrial adenocarcinomas, commonly metastasize to pelvic or paraaortic lymph nodes, leiomyosarcomas rarely spread to nodal sites.

In the review of 203 stage I and II carcinosarcomas surgically staged as part of a Gynecologic Oncology Group (GOG) study reported by Silverberg et al. (1990), nodal metastases were detected in 34 cases (16.7%). Lymph node metastases were identified in only 3.5% of patients with clinically localized leiomyosarcomas at the time of surgical staging in the GOG study. Data from three series indicate that lymph nodes were histologically positive only if clinically enlarged or associated with obvious intraabdominal spread. Thus, the need for lymph node dissection in patients with leiomyosarcomas remains unsubstantiated.

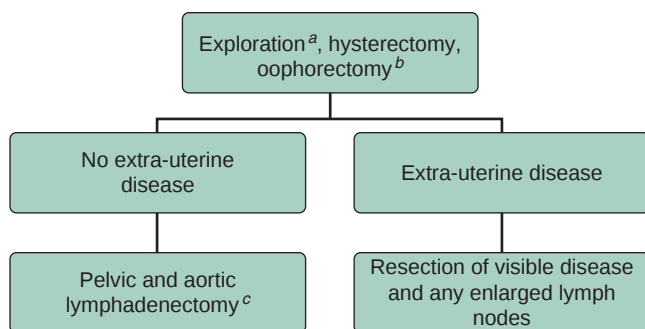


FIGURE 9.3. Initial management algorithm for patients with operable leiomyosarcoma, endometrial stromal sarcoma, and high-grade undifferentiated sarcoma. ^aExploration can be performed via laparotomy or laparoscopy based on clinical judgment. ^bThe need for oophorectomy can be tailored to patient's reproductive status but is encouraged for ESS. ^cLymphadenectomy is not required for uterine-confined LMS and ESS. (Adapted from NCCN practice guidelines in oncology v.2.2009; UTSARC-1.)

PATHOLOGY

Malignant mesenchymal tumors can be classified into pure mesenchymal tumors and tumors with a mixed epithelial and mesenchymal component. In the first group, the most common is leiomyosarcoma, followed by endometrial stromal sarcoma, and rarely others including rhabdomyosarcoma, liposarcoma, angiosarcoma, chondrosarcoma, osteosarcoma, and alveolar soft part sarcoma. Mixed epithelial and mesenchymal tumors include carcinosarcoma and adenosarcoma. In addition, there are two rare mesenchymal tumors occurring in the uterus: uterine tumors resembling ovarian sex cord tumors and perivascular epithelioid cell tumors (PEComas).

Leiomyosarcoma and Other Smooth Muscle Tumors

Leiomyosarcomas are malignant smooth muscle tumors that usually arise *de novo*. Recent studies have shown that some tumors show areas with benign morphology suggesting some progression from leiomyoma to leiomyosarcoma but clonality studies only support this progression in a small percentage of cases. Microscopically most leiomyosarcomas are overtly malignant and have hypercellularity, coagulative tumor cell necrosis, abundant mitoses (more than 10/10 hpf), atypical mitoses, marked cytologic atypia, and infiltrative borders. The three most important criteria are coagulative tumor cell necrosis, high mitotic rate, and significant cytologic atypia.

Some smooth muscle tumors have histologic features that are not worrisome enough to render an unequivocal diagnosis of sarcoma. These tumors can be classified as atypical leiomyomas, smooth muscle tumors

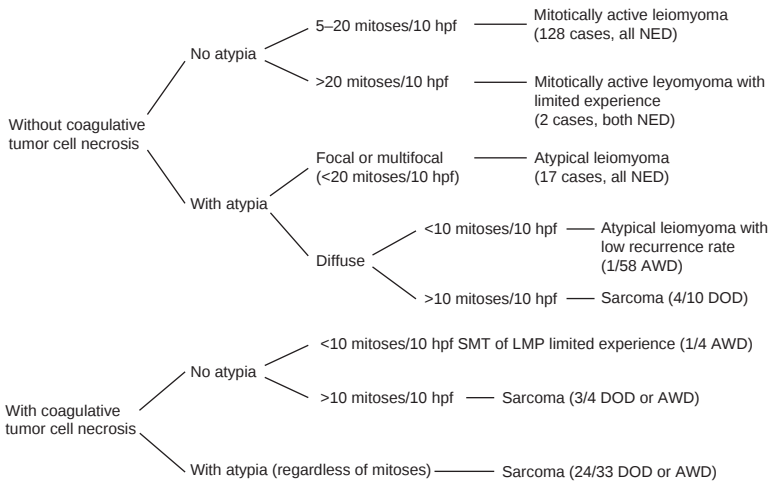


FIGURE 9.4. Uterine smooth muscle tumors (excluding epitheloid and myxoid types and cervical tumors).

AWD, alive with disease; DOD, dead of disease; hpf, high power fields; LMP, low malignant potential; NED, no evidence of disease; SMT, smooth muscle tumor.

with low malignant potential (low probability of an unfavorable outcome), or smooth muscle tumors of uncertain malignant potential (insufficient numbers have been studied to predict their behavior). Figure 9.4 summarizes the classification of uterine smooth muscle tumors based on their histologic characteristics. It is recommended that unusual cases be reviewed by a gynecologic pathologist. Histologic parameters of leiomyosarcomas that have been shown to be prognostic indicators include grade, mitotic rate, extensive tumor cell necrosis, and lymphovascular invasion. Estrogen and progesterone receptors are expressed in a large percentage of leiomyosarcomas (38% to 60%), but this does not seem to correlate with overall survival, nor does it suggest that hormonal therapy is beneficial.

Carcinosarcoma

Uterine carcinosarcomas, also called malignant mixed müllerian tumors, are lesions containing carcinomatous and sarcomatous elements. Numerous studies have shown that these tumors are clonal malignancies derived from a single stem cell and should be considered “metaplastic carcinomas.” Microscopically, the tumors have a typical biphasic pattern with carcinomatous and sarcomatous elements. The carcinoma is usually high-grade and the sarcomatous component is always high-grade and may be homologous or heterologous. Homologous elements are those components that are native to the uterine body and most commonly are high-grade fibrosarcoma, although other varieties such as undifferentiated sarcoma may be found as well. Heterologous elements are those components that

are not normally found within the uterus with the most common being rhabdomyosarcoma, followed by chondrosarcoma, and less often others. Heterologous elements are seen in half of the cases. The most common heterologous sarcoma is rhabdomyosarcoma, followed by chondrosarcoma, and less often osteosarcoma and liposarcoma.

Most studies suggest that the behavior of carcinosarcomas is predicted by the carcinomatous component. Tumors typically metastasize through lymphatic channels similar to endometrial carcinomas. Most metastases and recurrences are composed of pure carcinoma. In two recent studies, adverse prognostic factors included the following: heterologous elements (in stage I tumors), and high percentage of sarcomatous component in the main tumor and in the recurrences.

Endometrial Stromal Neoplasms

In the current World Health Organization classification, endometrial stromal tumors are classified into endometrial stromal nodules, endometrial stromal sarcomas (by definition low-grade), and undifferentiated endometrial sarcoma. Both endometrial stromal nodules and endometrial stromal sarcomas are composed of cells identical to those found in the stroma of proliferative endometrium. Undifferentiated endometrial sarcomas, on the other hand, are high-grade sarcomas that do not resemble endometrial stroma and diagnosis is by excluding other uterine sarcomas.

The differential diagnosis between an endometrial stromal nodule and an endometrial stromal sarcoma is important since the nodules are always benign lesions. Differential diagnosis is based upon the presence of infiltrating margins with or without angioinvasion in endometrial stromal sarcoma. These two features are not seen in stromal nodules, which are always well circumscribed and have pushing margins. It is impossible to render a definitive diagnosis based upon curettage material alone; final diagnosis requires a hysterectomy specimen.

Most endometrial stromal sarcomas have fewer than 10 mitoses/10 hpf, but even mitotically active variants behave in a similar indolent manner. Sixty percent of low-grade endometrial stromal tumors (including ESS and stromal nodule) have cytogenetic abnormalities involving rearrangements of chromosomes 6, 7, and 17. The most characteristic translocation of these tumors, t(T7;17) (Tp15;q21), generates a fusion of the JAZF1 and JJAZ1 genes both of which encode zinc finger proteins.

Undifferentiated endometrial sarcomas have cytologic atypia to the extent that they cannot be recognized as arising from endometrial stroma. Morphologically, these high-grade lesions resemble undifferentiated mesenchymal tumors and behave as high-grade sarcomas. It is advisable to use a term such as “high-grade sarcoma,” “undifferentiated sarcoma,” or “poorly differentiated uterine sarcoma” rather than “endometrial stromal sarcoma.” This last term may inaccurately suggest an indolent tumor. Undifferentiated uterine sarcomas are usually seen in patients older than 50 years, have a recurrence rate of over 85%, and are usually fatal.

Müllerian Adenosarcoma

Müllerian adenosarcomas are mixed müllerian tumors composed of malignant stromal and benign epithelial components. Microscopically, the tumors have a benign epithelial component usually covering the surface of the polyps and in the form of benign glands uniformly distributed throughout the tumor. The mesenchymal component is usually a low-grade sarcoma that resembles endometrial stroma. Minimal criteria include at least one of the following: two or more stromal mitoses/10 hpf, marked stromal hypercellularity, and significant stromal cell atypia. A minority of cases have “sarcomatous overgrowth,” when more than 25% of the tumor is composed of pure sarcoma. In these cases, the sarcoma is typically high-grade and the lesions are aggressive. Most adenosarcomas without stromal overgrowth express estrogen receptors in the sarcomatous component and this may be used for therapeutic purposes.

RADIATION THERAPY

KEY POINTS

- Radiation therapy for carcinosarcoma and leiomyosarcoma can provide good local control, but does not impact overall survival due to distant failure.
- Radiation therapy is not indicated for endometrial stromal sarcoma.

Since the utilization of radiation therapy for patients with uterine sarcomas has been almost exclusively in the postoperative setting, the role of primary or palliative radiotherapy will not be presented. As they are more fully explored in the chapter on epithelial tumors of the corpus, a detailed discussion of the techniques and complications of adjuvant radiation therapy will not be discussed in this section (Fig. 9.5).

Uterine Sarcomas

Most of the published papers on sarcomas of the uterus have been retrospective in nature, often requiring many years, if not decades, to accumulate enough patients to perform meaningful statistical analyses. Furthermore, these studies have often had to combine many types of sarcomas to attain numbers sufficient for evaluation. Thus, most of these retrospective studies have not achieved statistical power to reach definite conclusions. However, the data from the non-randomized review of the Surveillance, Epidemiology, and End Results (SEER) analyses of 2,677 cases of all types of uterine sarcomas did demonstrate a statistically significant improvement in survival favoring adjuvant radiotherapy for stage II, III, and IV (but not stage I) uterine sarcomas.

The GOG has previously conducted two prospective clinical trials involving selected patients with uterine sarcomas. The earliest study

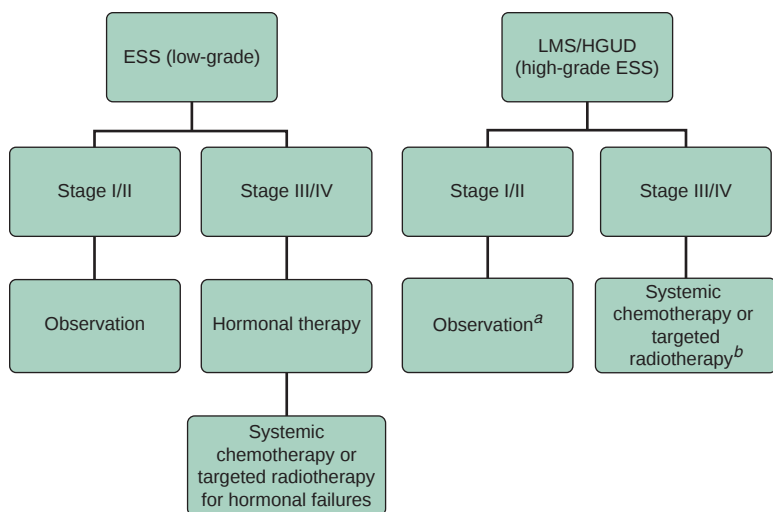


FIGURE 9.5. Adjuvant management algorithm for patients with leiomyosarcoma, endometrial stromal sarcoma, and high-grade undifferentiated sarcoma. ^aConsider adjuvant chemotherapy or pelvic RT for particularly high-risk features. ^bFor isolated extrauterine disease tumor-directed RT may be appropriate, but in general systemic chemotherapy should be given for advanced stage disease. (Adapted from NCCN practice guidelines in oncology v.2.2009; UTSARC-2/3.)

reported on 156 evaluable patients with surgically staged I or II sarcomas of the uterus (GOG-20). Radiotherapy did not seem to affect recurrence in general. However, there was a notable decrease in vaginal recurrences in patients with carcinosarcomas. Furthermore, there was a significant reduction in pelvic relapses (10%) in treated patients compared with those untreated (23%) (Table 9.1). The second main GOG trial for patients with uterine sarcomas involved a clinicopathologic evaluation of patients with clinical stage I and II diseases (GOG-40). Although adjuvant pelvic external beam therapy was not mandated in this surgical trial, there appeared to be a possibility that adjuvant radiation plays a role in reducing pelvic relapses.

Currently, there is one completed prospective phase III clinical trial that focused on the role of adjuvant radiation therapy for patients with all three main cell types of uterine sarcomas (protocol 55874 of the European Organization for Research and Treatment of Cancer [EORTC]). Those subjects in EORTC 55874 with surgical stage I or II disease were randomized to either no further treatment or external beam irradiation of the whole pelvis. For carcinosarcomas, there were 2 of 46 (4.4%) in the adjuvantly irradiated arm and 11 of 45 (24.4%) in the observation subset with isolated local relapses. For leiomyosarcomas, 1 of 50 (2%) in the radiotherapy group and 7 of 49 (14.3%) in the untreated cohort developed isolated local

TABLE 9.1

SITES OF FIRST RECURRENCE^a

	Pelvic	Extra-pelvic
No RT	14/60 (23%)	12/60 (20%)
Pelvic RT	5/49 (10%)	17/49 (35%)

^a85% of this group (93 patients) with nonleiomyosarcomas of the uterus were stage I/II uterine carcinosarcomas.

RT, radiation therapy.

Source: Modified from Hornback NB, Omura G, Major FJ. Observations on the uterine sarcomas of adjuvant radiation therapy in patients with stage I and II uterine sarcoma.

Int J Radiat Oncol Biol Phys. 1986;12:2127–2130.

failures. Though local control was improved in both subtypes, patients with isolated local failures evaluated in EORTC 55874 are in the minority for both carcinosarcomas and leiomyosarcomas. The patients treated post-operatively had a nonsignificant median survival advantage of 8.5 years versus 6.7 years for the observational cohort with a hazard ratio of 1.02 (95% confidence interval [CI]: 0.68 to 1.53, $p = 0.92$).

Uterine Carcinosarcomas

Other reports have been limited to one histologic type of sarcoma. The most common of these have evaluated uterine carcinosarcomas. Results are inconsistent with some studies demonstrating no benefit for radiotherapy, while others have shown a significant impact of adjuvant pelvic radiotherapy on the survival for patients with carcinosarcomas. One of these studies involved a review of the nonrandomized SEER database of 2,461 women with carcinosarcomas from 1973 to 2003. In this data set, 890 patients received adjuvant radiotherapy. The overall 5-year survival rates of those receiving radiotherapy versus no irradiation were 41.5% and 33.2%, respectively ($p < 0.001$). Furthermore, a significant improvement in survival in this study was observed for all stages of disease, including stage IV. Finally, there have been several published retrospective reports suggesting that combined adjuvant radiotherapy and chemotherapy may impart even longer survival, especially for stage I and II diseases.

There has been one randomized phase III prospective trial of adjuvant radiotherapy in carcinosarcomas, protocol 150 conducted by the GOG. This study compared whole abdominal irradiation to three cycles of cisplatin-ifosfamide chemotherapy with respect to recurrence rates, disease-free and overall survival. Eligible were patients with carcinosarcomas confined to the abdomen who underwent optimal surgical debulking with no post-surgical residual disease greater than 1 cm. After adjusting for stage and age at diagnosis, there was a diminution in death rate reduction to 23% for

TABLE 9.2

PATTERNS OF FAILURE

Sites of Recurrence ^a	WAI (<i>n</i> = 105), Number of Cases	Chemotherapy (<i>n</i> = 101), Number of Cases
Vagina	4	10
Pelvis	14	14
Abdomen	29	19
Distant	27	24

^aSome patients had multiple sites of relapse.

n, total number of cases in each arm; WAI, whole abdominal irradiation.

Source: Modified from Wolfson AH, Brady MF, Rocereto T, et al. A Gynecologic Oncology Group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as postsurgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. *Gynecol Oncol.* 2007;107:177–185.

those receiving chemotherapy compared with radiotherapy (HR = 0.712, 95% CI: 0.484 to 1.048, *p* = 0.085, two-tail test). Of interest is the fact that those patients who received adjuvant radiotherapy had more late complications, mainly gastrointestinal, than those having cytotoxic therapy (*p* < 0.001). In addition, two patients undergoing radiotherapy died as a direct result of radiation-induced hepatitis.

Based upon the results of GOG protocol 150, the role of adjuvant radiotherapy for the management of patients with carcinosarcomas continues to remain uncertain. Since there were more vaginal failures in the chemotherapy arm of GOG protocol 150 and other sites of relapse were similar or less common in frequency (abdominal recurrences) than those in the radiotherapy arm, perhaps postoperative vaginal brachytherapy (either high- or low-dose rate) with chemotherapy should be considered for any patient having optimally debulked carcinosarcomas in future trials (Table 9.2).

Uterine Leiomyosarcomas

The second most frequent type of uterine sarcomas is leiomyosarcomas. The overall pelvic/extra-pelvic relapse rates are approximately 16.6% and 42.0% for patients with uterine leiomyosarcoma. There still remains a paucity of information that specifies between upper abdominal and extra-abdominal distant sites of tumor involvement. The respective pelvic/extra-pelvic percentages were 18.5% [22/119]/41.2% [49/119] for nonirradiated and 12.9% [8/62], 43.5% [27/62] for patients treated with postoperative radiotherapy. From this overview, it does not appear that postoperative radiotherapy has any real effect on reducing recurrences for patients with uterine leiomyosarcoma.

However, two of the listed series combined to yield an 11.1% [4/36] pelvic relapse rate with radiation versus 61.1% [22/36] without the implementation of adjuvant radiation therapy. Yet, the major problem is that the majority of these patients have distant extra-abdominal metastases, such as the lung, despite having local control. This would suggest that adjuvant systemic therapy must be added in order to have an impact on the outcome of these patients.

Endometrial Stromal Sarcomas

The total pelvic and extrapelvic rates of relapse for patients with endometrial stromal sarcomas are 42.2% and 33.3%, respectively. There was a 33.3% [6/18] pelvic recurrence rate of which the majority did not undergo any radiation therapy. This latter finding initially suggested that postoperative external pelvis radiotherapy could be considered for the subset of patients with low-grade ESS.

A more recent report retrospectively reviewed 28 patients with endometrial stromal sarcomas of which 19 were low-grade and 9 high-grade. Fifty percent of the patients in this series underwent adjuvant pelvic radiotherapy with no difference in the survival of the patients. In addition, almost 30% of those receiving adjuvant radiotherapy relapsed within the treatment field. Thus, unless vaginal brachytherapy finds a niche, there appears no definite indication for postoperative radiotherapy for patients with these high-grade lesions.

CHEMOTHERAPY

KEY POINTS

- Combined chemotherapy is more effective than single agents.
- Active agents are different for carcinosarcoma and leiomyosarcoma.
- Hormonal therapy is effective for endometrial stromal sarcoma.

Uterine sarcomas, although far less common than endometrial carcinomas, exhibit two features that increase the need for systemic therapy: a recurrence rate of at least 50%, even in early-stage disease, and a high propensity for distant failure. The comparatively low incidence of uterine sarcomas has made randomized controlled trials difficult. Crucial to the understanding of the use of chemotherapy in uterine sarcomas is the observation that these neoplasms are heterogeneous. The first two subtypes, carcinosarcomas and leiomyosarcomas, constitute 90% of cases entered into clinical trials. These two histologic subtypes are usually the only uterine sarcomas with sufficient numbers to permit meaningful phase III studies; however, as these two histologic subtypes appear to respond differently to chemotherapy, they should be studied separately (Fig. 9.5).

Chemotherapy: Limited Disease

Uterine sarcoma has a high rate of distant metastases even in the absence of intraperitoneal or lymph node metastases. It has been concluded that this is due to the high rate of hematogenous and lymphatic dissemination. Even for surgical stage I disease, the recurrence is as high as 53%. Although the recurrent rate and median survival of patients treated with doxorubicin compared to no therapy were 39% versus 51% and 73 months versus 55 months, respectively, this GOG trial which did not segregate different histologic subtypes concluded that there was no significant difference. As with advanced disease, more recent trials began to segregate the histologic subtypes. A GOG study reported by Sutton et al. in 2005, 65 patients with completely resected stage I and II carcinosarcomas of the uterus were treated with adjuvant ifosfamide and cisplatin. The 2- and 5-year survival rates were 82% and 62%, respectively. Since more than half of the recurrences involved the pelvis, the study suggested that a combined sequential approach with chemotherapy and radiotherapy might be beneficial for this group of patient, which should be verified in randomized phase III study.

To date, there have been no separate prospective studies on patients with uterine leiomyosarcomas. Two factors continue to limit the study of adjuvant therapy in patients with uterine leiomyosarcomas: the relatively low frequency of the disease, which makes it difficult to complete randomized trials in a reasonable period of time, and the lack of highly active agents. A phase II adjuvant therapy trial of gemcitabine and docetaxel followed by doxorubicin for women with high-risk leiomyosarcoma has recently completed accrual through the Sarcoma Alliance for Research through Collaboration.

Chemotherapy: Advanced or Recurrent Disease

Leiomyosarcomas

Numerous single agents have been and continue to be tested in patients with leiomyosarcomas. Doxorubicin and ifosfamide are the most active agents investigated as primary single agent chemotherapy in recurrent and advanced uterine leiomyosarcomas. Combination chemotherapy yields greater response rates.

In 1996, using a combination of ifosfamide and doxorubicin, the GOG demonstrated an overall response of 30.3% in patients with advanced leiomyosarcoma with no history of prior treatment. Gemcitabine plus docetaxel was proven highly active and tolerable (53% overall response rate) in treated and untreated patients with leiomyosarcomas. Given the paucity of survival data available from the randomized trials to compare various chemotherapy regimens, a pooled analysis showed that patients who received first or second line chemotherapy for the treatment of metastatic leiomyosarcoma had a higher response rate with combination chemotherapy than with single agent chemotherapy.

Uterine Carcinosarcomas

Several drugs have been studied in this group of tumors as single agents. However, only three drugs have demonstrated clear-cut activity: ifosfamide, cisplatin, and paclitaxel. Of the three drugs given as a single agent, ifosfamide is the most active single agent studied to date. In patients with prior chemotherapy, cisplatin produced an 18% response in 28 patients. A repeat trial in patients with no prior chemotherapy documented essentially the same response rate of 19% among a larger group of patients. Paclitaxel, as a single agent, was associated with a response rate of 21.2% in a group of 33 patients with uterine sarcoma who had prior chemotherapy, with an 8.2% response rate in patients who failed appropriate local therapy. Doxorubicin, generally regarded as the most active agent in soft tissue sarcomas, unfortunately demonstrated inconsistent activity in three trials of patients with carcinosarcomas.

The GOG evaluated the addition of cisplatin to ifosfamide in 194 eligible carcinosarcoma patients and found that this improved the overall response rate from 36% to 54% and prolonged the median progression-free interval by an absolute 2 months. However, this advantage was not associated with a significant overall survival gain. More recently and based upon the finding of moderate activity (18% response rate) of paclitaxel for this disease, the GOG carried out a phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcomas. The group found that the addition of paclitaxel produced a 45% response rate compared with 29% in the ifosfamide single agent arm with overall survival significantly improved. There was a significant decrease in the hazard of death and progression but more sensory neuropathy, as expected. There is moderate evidence to support the use of combination chemotherapy in advanced or recurrent uterine carcinosarcomas. Combination regimens, which result in significant improvements in survival, are needed.

Endometrial Stromal Sarcoma

Randomized phase III trials with stromal sarcomas are limited due to the rarity of this disease. The GOG reported a phase II study of ifosfamide treatment in 21 cases with high- or low-grade, recurrent or metastatic endometrial stromal sarcomas with an overall response 33.3%. Another non-controlled study observed a 50% response rate to doxorubicin therapy in ten patients with recurrent endometrial stromal sarcomas. Interest in endometrial stromal sarcomas continues owing to the difference in the prognosis of patients with low-grade disease versus those with undifferentiated endometrial sarcomas. In recurrent stromal sarcoma, reports support hormone therapy for patients with low-grade subgroup and chemotherapy for high-grade tumors. Current definitions do not include high-grade lesions as a component of endometrial stromal sarcoma.

Hormonal Therapy

Although the role of hormonal therapy is clear in breast and endometrial cancers, few uterine sarcomas contain sufficient estrogen- or progesterone-receptor

protein to influence therapy, the only exception being low-grade endometrial stromal sarcomas or stromal nodules. Uniquely, low-grade endometrial stromal sarcomas are hormonally responsive in roughly two-thirds of cases and long-term maintenance therapy should be beneficial. Progestins, gonadotropin-releasing hormone analogues, or aromatase inhibitors have been used in the treatment of patients with advanced or recurrent stromal sarcomas. Several papers reported that long-term use of tamoxifen for the treatment of breast cancer was related to the development of uterine sarcomas. Hormonal therapy has not been extensively evaluated in mesenchymal uterine tumors.

Systemic Therapy Summary

The current role of chemotherapy in the management of uterine sarcomas involves the treatment of patients with advanced or recurrent disease, and an emphasis on palliative intent. In leiomyosarcomas, the active drugs are doxorubicin, ifosfamide, gemcitabine, and docetaxel. For carcinosarcomas, the drugs of choice are ifosfamide, cisplatin, and paclitaxel. Hormonal therapy, including progestational agents, gonadotropin-releasing hormone analogues, and aromatase inhibitors, may have a role in the treatment of advanced or recurrent endometrial stromal sarcomas. The use of hormonal agents in the treatment of other histologic subtypes has not been well studied.

LONG-TERM RESULTS OF THERAPY

Leiomyosarcoma

The prognosis of patients with uterine leiomyosarcoma is uniformly poor. The reported 5-year survival of uterine leiomyosarcoma varies between 30% and 48%. However, leiomyosarcoma may tender a worse prognosis than carcinosarcoma when adjusting for stage and mitotic count. The mitotic index was the only factor significantly related to progression-free interval.

Carcinosarcomas and Müllerian Adenosarcomas

Major et al. (1993) reported a recurrence rate of 53% for 301 patients with clinical stage I and II carcinosarcomas. This included 61 patients (20%) who were “upstaged” based upon surgical findings. The prognostic factors based on multivariate analysis were adnexal spread, lymph node metastases, histologic cell type, and grade of sarcoma. Median survival in patients with clinically recurrent or advanced-stage carcinosarcomas ranged from 4 to 13 months despite therapy.

Among the 100 adenosarcoma patients, 26.1% developed recurrent disease. Generally, müllerian adenosarcomas are regarded as locally invasive; however, sarcomatous overgrowth has been described in as many as 57% of cases and is associated with a fulminant clinical course and death.

Endometrial Stromal Sarcoma

Virtually no endometrial stromal nodule will recur after hysterectomy. In comparison with leiomyosarcoma and carcinosarcoma, patients with endometrial stromal sarcoma tend to present with low-grade and early-stage disease with favorable prognosis. In a large series, mitotic count successfully predicted outcome in patients with stage II to IV endometrial stromal sarcomas. Young et al. and Berchuck et al. have suggested that patients with ovarian preservation at the time of hysterectomy for endometrial stromal sarcoma were more likely to develop recurrences. Bilateral salpingo-oophorectomy would seem to be prudent given the potential for low-grade endometrial stromal sarcomas to express estrogen receptors and respond to hormonal therapy.

Patterns of Failure

A propensity for carcinosarcoma to relapse in the abdomen or pelvis and leiomyosarcomas to metastasize to the lung has been reported. In the follow-up of the GOG staging study reported by Major et al. (1993), 28 of 301 patients with carcinosarcoma developed lung metastases (9.3%) versus 24 of 59 (40.7%) of those with leiomyosarcomas. Recurrences with a pelvic component were 63 (20.9%) and 8 (13.6%), respectively, for the two tumor types. In patients whose tumors were initially confined to the uterus, there were purely distant recurrences in only 4 of 51 (7.8%) patients with carcinosarcoma but 22 of 35 (62.9%) in the patients with leiomyosarcoma.

CONCLUSIONS

There has been a slow evolution in the understanding of the basic science of sarcomas. The majority are felt to be sporadic with no specific etiology and most have complex karyotypes. However, in an increasing number of sarcomas, specific chromosomal translocations resulting in fusion genes that are constitutive and involve the activation of transcription factors have been identified.

Trials of adjuvant chemotherapy are appropriate in early stage, resected leiomyosarcomas. Recurrence rates after surgery alone are unacceptably high; the risk of mortality associated with recurrent leiomyosarcoma easily offsets any morbidity derived from adjuvant chemotherapy in this population of relatively young patients. Combination or sequential radiation and chemotherapy have a great deal of appeal. A basic understanding of uterine sarcomas and their differences is paramount to the understanding of surgical and adjuvant therapy as well as palliative treatment in patients with these rare neoplasms; this knowledge is critical in the practice of gynecologic oncology.

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CHAPTER 10 ■ OVARIAN CANCER (INCLUDING THE FALLOPIAN TUBE)

Ovarian cancer is the eighth most common major cancer and the fifth most common cause of cancer death in U.S. women. It has been estimated that, in the United States, 1 woman in 70 will develop ovarian cancer, and 1 woman in 100 will die of the disease.

Worldwide, ovarian cancer is the sixth most common form of cancer in women. In general, the highest incidence rates are found among European and North American population groups with the lowest rates in Asian population groups. In the United States, rates for black American women are about two thirds of those for white women, and rates for women of Asian/Pacific Islander descent are similar to those of black women. Rates of hysterectomy and oophorectomy in a population will affect the rate of ovarian cancer; 40% to 50% of women in the United States have a hysterectomy by 60 to 70 years of age, and about half of them have their ovaries removed at the same time.

Despite some apparent advances in therapy, survival in the United States from ovarian cancer has increased only slightly over the past decades. Small but significant improvements in survival have been noted for white women but not for black women. Overall 5-year relative survival rates were 45% for whites and 39% for blacks during 1996 to 2002. Outcomes in black women are worse even when controlling for age, stage, and histology.

RISK FACTORS

KEY POINTS

- Ovarian cancer is the fifth most common cause of death in U.S. women.
- Risk factors for ovarian cancer include increasing age, nulliparity, and family history.
- Use of oral contraceptives and tubal ligation are protective.
- Carriers of a BRCA1 or 2 mutation have a 20% to 40% lifetime risk of ovarian cancer, and should be considered for prophylactic salpingo-oophorectomy.

Established risk factors for ovarian cancer include increasing age, family history, nulliparity, early menarche, and late menopause. Breast feeding is protective. Aside from having a first degree relative with the disease, age is the most important risk factor for ovarian cancer (Fig. 10.1). Fifty percent

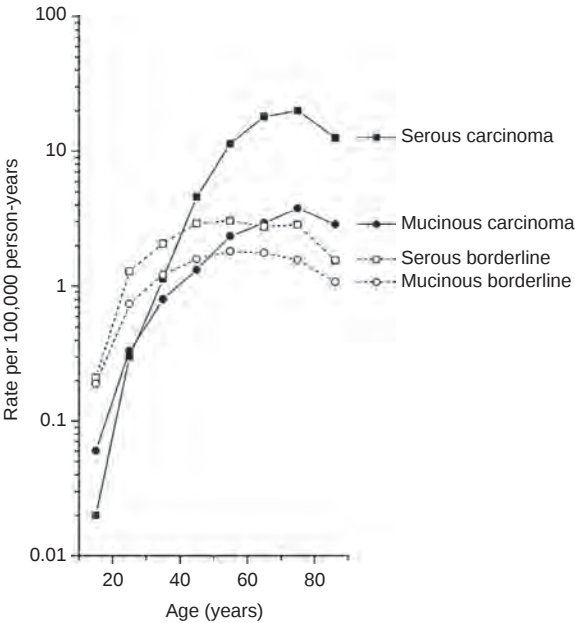


FIGURE 10.1. Incidence of invasive and borderline ovarian tumors in the United States by age.

Source: Sherman ME, Berman J, Birrer MJ, et al. Current challenges and opportunities for research on borderline ovarian tumors. *Hum Pathol.* 2004;35:961–970.

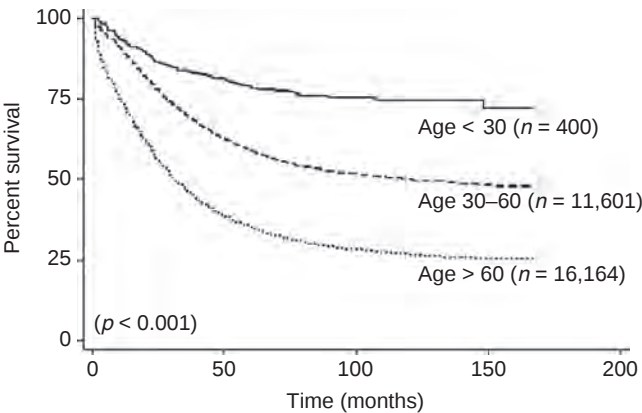


FIGURE 10.2. Disease-specific survival of patients based on age at diagnosis.

Source: Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs. older women: A population-based analysis. *Br J Cancer.* 2006;95:1314–1320.

of all U.S. cases occur in women over the age of 65. Older women have a much worse prognosis overall (Fig. 10.2), which is in part because they have an increased incidence of high stage and high-grade disease at the time of diagnosis (Table 10.1). However age remains a poor prognostic factor even when results are adjusted for stage, grade, histologic cell type, race, and surgical treatment.

There have been no consistent relationships reported of specific dietary components to ovarian cancer risk. Although some studies had implicated a diet high in meat and animal fat or a diet high in lactose, most large recent studies have failed to demonstrate any relationship between the consumption of animal foods and the development of ovarian cancer. There does appear to be a modest inverse correlation between moderate physical activity and ovarian cancer risk, and obesity has consistently shown a positive association with ovarian cancer risk.

Case-control analyses have consistently documented that users of oral contraceptives (OCP) have a 30% to 60% smaller chance of developing ovarian cancer than do women who have never used OCP. Tubal ligation is also protective. Some reports have suggested an increased risk with use of fertility-inducing drugs such as clomiphene, but most recent studies have found either a weak association or no association between infertility treatment and development of ovarian cancer. There appears to be a modest association between hormone replacement therapy (HRT) and risk of ovarian cancer. Progestins have been proposed to be protective against ovarian cancer, and the risk of ovarian cancer may be greater for estrogen-only HRT than for estrogen-progestin combinations.

TABLE 10.1

**INCIDENCE OF STAGE AND GRADE BY
AGE GROUPING IN SEER DATA 1988 TO 2001**

	Total (<i>n</i> = 28,165)	Age < 30 (<i>n</i> = 400)	Age 30–60 (<i>n</i> = 11,601)	Age > 60 (<i>n</i> = 16,164)
STAGE				
I	22%	58%	31%	15%
II	8%	8%	9%	8%
III	36%	19%	34%	38%
IV	34%	16%	26%	40%
GRADE				
1	9%	34%	12%	5%
2	18%	24%	21%	16%
3	44%	13%	44%	45%
Unknown	29%	29%	23%	34%

Source: Adapted from Chan JK, Urban R, Cheung MK, et al. Ovarian cancer in younger vs. older women: A population-based analysis. *Br J Cancer*. 2006;95:1314–1320.

Approximately 10% of cases of invasive epithelial ovarian cancer are estimated to be the result of autosomal dominant high-penetrant genetic factors, predominantly germ-line mutations in the BRCA1 or the BRCA2 genes. The BRCA gene products appear to function in the cellular response to certain types of DNA damage. The lifetime risk of ovarian cancer for women with BRCA1 mutations and BRCA2 mutations has been estimated to be 40% and 20%, respectively. Risk may be reduced by prophylactic salpingo-oophorectomy. Survival for women with ovarian cancer related to a BRCA mutation has been reported to be longer than for women with a similar stage cancer and no mutation. Issues related to BRCA mutations as well as mutations in genes involved in the mismatch repair pathway are discussed in Chapter 3, “Clinical Genetics of Gynecologic Cancers.”

PATHOLOGY

KEY POINTS

- The majority of fatal ovarian cancers in the United States are high-grade serous neoplasms.
- Borderline tumors are usually confined to the ovary and have an excellent prognosis.
- Primay mucinous ovarian cancers are difficult to distinguish from metastases to the ovary from other sites.

Ovarian carcinoma includes many subtypes (Table 10.2). The vast majority of fatal ovarian cancers are high-grade serous carcinomas. These tumors are believed to arise *de novo* from the surface epithelium of the ovary or perhaps from the mucosa of the fallopian tube, and progress rapidly. This makes screening and early detection difficult. Most of the remaining cell types of ovarian carcinomas appear to follow an adenoma–carcinoma sequence. Nearly all clear cell carcinomas and a large proportion of endometrioid carcinomas arise in endometriosis, and appear to progress through an adenoma (or hyperplasia)–borderline tumor–carcinoma sequence. Similarly, mucinous carcinomas most probably transit through a mucinous cystadenoma–borderline tumor–intraepithelial carcinoma sequence before invasion occurs. Such tumors are much more likely to be diagnosed while still confined to the ovary, and they therefore comprise most curable ovarian carcinomas. Low-grade serous carcinoma is a recently described and relatively small subset of ovarian serous carcinoma that also often appears to follow a stepwise progression from borderline tumor to invasive carcinoma.

Serous Tumors

About 20% of serous tumors are malignant, 2% are borderline tumors, and about 78% are benign. The mean age for patients with cancer is 56 years. Patients with benign and borderline tumors are generally younger, with

TABLE 10.2**HISTOLOGIC CLASSIFICATION OF COMMON
EPITHELIAL TUMORS OF THE OVARY****SEROUS TUMORS*****Benign***

Cystadenoma and papillary cystadenoma
 Surface papilloma
 Adenofibroma and cystadenofibroma
 Borderline tumor (atypical proliferative tumor)
 Cystadenoma and papillary cystadenoma
 Surface papilloma

Malignant

Adenocarcinoma
 Surface papillary adenocarcinoma
 Malignant adenofibroma and cystadenofibroma

MUCINOUS TUMORS***Benign***

Cystadenoma
 Adenofibroma and cystadenofibroma
 Borderline tumor (atypical proliferative tumor)
 Intestinal type
 Endocervicallike

Malignant

Adenocarcinoma
 Malignant adenofibroma
 Mural nodule arising in mucinous cystic tumor

ENDOMETRIOID TUMORS***Benign***

Adenoma and cystadenoma
 Adenofibroma and cystadenoma
 Borderline tumor (atypical proliferative tumor)

Malignant

Adenocarcinoma
 Adenoacanthoma
 Adenosquamous carcinoma
 Malignant adenofibroma with a malignant stromal component
 Adenosarcoma
 Endometrial stromal sarcoma
 Carcinosarcoma, homologous and heterologous
 Undifferentiated sarcoma

CLEAR CELL TUMORS***Benign***

Borderline tumor (atypical proliferative tumor)

(continued)

TABLE 10.2

**HISTOLOGIC CLASSIFICATION OF COMMON
EPITHELIAL TUMORS OF THE OVARY** (*continued*)

<i>Malignant</i>
Adenosarcoma
TRANSITIONAL CELL TUMORS
Brenner tumor
Proliferating Brenner tumor
Malignant Brenner tumor
Transitional cell carcinoma (non-Brenner type)
Squamous cell carcinoma
MIXED EPITHELIAL TUMORS (SPECIFY TYPES)
<i>Benign</i>
Borderline tumor (atypical proliferative tumor)
<i>Malignant</i>
Undifferentiated carcinoma

Source: Modified with permission from Tavassoli FA, Devilee P. *Tumours of the Breast and Female Genital Organs*. World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2003:114.

mean ages at diagnosis of 45 and 48 years, respectively. Approximately one in six serous adenomas is bilateral. Serous borderline tumors and stage I serous adenocarcinomas are bilateral in one third of cases. Those of higher stage are bilateral in two thirds of cases. Borderline tumors that are confined to the ovary are associated with a survival that approaches 100%. The 10-year survival for women with tumors that have associated noninvasive peritoneal lesions still exceeds 95%, while for those with invasive implants it is 67%. Micropapillary serous tumors are a subtype of borderline tumors that are particularly likely to be associated with invasive implants and therefore have a worse prognosis. Microinvasion (defined variously as a maximal invasive focus size of 2, 3, or 5 mm, or an area of 10 mm²) can be found in up to 10% of borderline tumors. The overall prognosis for the patient with microinvasion in a borderline tumor is currently considered to be no different than that of a borderline tumor without microinvasion. Borderline serous tumors may also spread to lymph nodes, but this does not appear to worsen the overall good prognosis.

Serous adenocarcinomas range in size from small (2 to 3 cm) to quite large. They often present as solid masses bounded by a capsule, often containing areas of necrosis and hemorrhage. The ovary from which the neoplasm has arisen is frequently not apparent grossly or microscopically. The gross appearance of a typical high-grade serous carcinoma is not distinctive, and it may be mimicked by other high-grade epithelial ovarian neoplasms, granulosa cell tumors, and carcinomas metastatic to the ovary. The tumor may appear as large sheets of polygonal cells growing autonomously

without stromal support or as broad to fine clusters of cells related to papillae that irregularly dissect through the stroma, accompanied by a host desmoplastic response. The nuclei are typically large and pleomorphic, with variably sized nucleoli, and numerous mitotic figures. Two grading systems for serous carcinomas have been proposed and tested in the past decade: a three grade system and more recently, a binary system of high-grade and low-grade serous carcinoma. In contrast to high-grade serous carcinoma, low-grade neoplasms are characterized by cells with only mild to moderate nuclear atypia, evenly distributed chromatin, variable nucleoli, and fewer than 10 mitoses/10 hpf. A micropapillary architecture is frequently observed. The binary system separates over 90% of advanced-stage serous carcinomas into the high-grade group. This distribution is reflected in the overall behavior of advanced-stage serous carcinoma, which is associated with a 5-year survival of about 25%. In contrast, the 5- and 10-year survivals for women with advanced-stage low-grade serous carcinoma are about 85% and 50% to 60%, respectively. Serous carcinomas nearly always stain positively with immunohistochemistry for WT1, cytokeratin (CK) 7, and negative or only focally positive for CK20 and calretinin. A panel that includes these antibodies is frequently employed to evaluate a carcinoma whose primary site is uncertain. Pancreatic and breast carcinomas have the same CK7/20 profile, and thus other markers are needed for these sites. GCDFP-15 (gross cystic disease fluid protein) is often positive in breast carcinoma and only rarely positive in ovarian carcinoma.

Mucinous Tumors

Primary ovarian mucinous tumors include three types: cystadenomas (81%; these are benign), borderline tumors (13%), and primary ovarian mucinous carcinomas (5%). The mean age for patients with mucinous adenocarcinoma is 52 years, which, as with serous adenocarcinoma, is greater than the mean age of patients with benign and borderline tumors (44 and 49 years, respectively).

Mucinous tumors can grow to extremely large sizes, being among the largest of any recorded tumor in the body. Sizes exceeding 40 kg and 30 cm in greatest diameter are not uncommon. There are two types of borderline mucinous tumors: the gastrointestinal type and the endocervical type. The gastrointestinal type is more common. Both types of borderline mucinous tumors are almost always stage I and have close to 100% survival. As with serous borderline tumors, the presence of microinvasion does not appear to affect the generally benign prognosis of these tumors.

Primary ovarian mucinous carcinomas are typically unilateral multicystic mucinous masses with smooth capsules. They may contain solid areas and regions of necrosis and rupture with surface involvement can occur. A thick tenacious mucinous material may fill the cysts. Most are stage I cancers. Pseudomyxoma peritonei, a clinicopathologic syndrome in which mucinous ascites is accompanied by low-grade neoplastic mucinous epithelium intimately associated with pools of extracellular mucin and fibrosis, was formerly thought to sometimes result from mucinous ovarian tumors, but

currently it is believed to universally be derived from appendiceal low-grade (adenomatous) mucinous tumors; the ovarian involvement is secondary.

Mucinous carcinomas with secondary spread to the ovary are much more commonly encountered than primary ovarian mucinous carcinomas, and the distinction can be difficult to make. The ovarian metastasis may be the presenting site of disease. Metastatic mucinous carcinomas are usually readily recognized as such when the ovarian tumors exhibit any or all of the following features: bilaterality, smaller size (typically < 10 cm), ovarian surface involvement, a nodular pattern of involvement, and an infiltrative pattern of stromal invasion. However, some metastatic mucinous carcinomas, especially those derived from the colorectum, pancreaticobiliary tract, appendix, and endocervix, can exhibit deceptive patterns of invasion. Immunohistochemical analysis with antibodies such as CK7, CK20, CDX-2, and p16 can be useful for identifying some metastatic mucinous carcinomas; however, the utility of currently available markers is limited due to overlapping immunoprofiles of primary ovarian mucinous tumors with other mucinous tumors, particularly those of upper gastrointestinal tract origin.

Endometrioid Tumors

Endometrioid tumors account for a relatively small proportion of the common epithelial tumors, but most endometrioid tumors are malignant. When controlled for stage, the survival rate for endometrioid tumors is similar to that of serous adenocarcinoma in some studies but better in others. About 10% to 40% of cases are associated with endometriosis. Over 10% of endometrioid tumors of the ovary are also associated with endometrial tumors of an identical histologic variant, each appearing as if it were primary in its respective organ. The similar histology and subtype and high survival rate of these patients (80% at 10 years) suggest that the majority are synchronous primaries rather than metastases. Many of these patients also have coexisting endometriosis.

Clear Cell Tumors

Clear cell tumors are uncommon in the United States; they are more common in Japan. About half of cases are associated with endometriosis. Clear and “hobnail” cells are the microscopic hallmark, but the diagnosis rests upon architecture as well as optically clear cytoplasm. When present, the clear appearance of the cytoplasm results from glycogen that has leached as the tissue specimen is prepared for microscopic examination. The hobnail cells contain bulbous nuclei that protrude into the lumen at the apparent cytoplasmic limits of the cell.

Mixed Carcinoma

Perhaps as many as 10% of all ovarian tumors of common epithelial origin are mixed, when defined as a carcinoma in which more than 10% of the neoplasm exhibits a second histologic cell type. One common specific

malignant combination is mixed clear cell and endometrioid carcinoma, both being related to endometriosis.

Primary Peritoneal Serous Carcinomatosis

Primary peritoneal carcinoma has been defined by the Gynecologic Oncology Group (GOG) as follows: (i) ovaries are of normal size or enlarged by a benign process; (ii) ovarian involvement is absent or limited to the surface and/or superficial cortex with no tumor nodule within the ovarian cortex exceeding 5×5 mm; (iii) serous histology; and (iv) volume of extraovarian disease significantly exceeds that of ovarian disease. The pathology and response to the treatment of peritoneal serous carcinomas are essentially identical to that of ovarian serous carcinomas. It has recently become apparent that the tubal fimbriae may be an important source of carcinomatosis in the absence of the typical features of primary tubal carcinomas (i.e., a dilated fallopian tube with a large mucosal lesion). Furthermore, the intramural portion of the tube is not removed if there is no hysterectomy, and therefore this segment is theoretically a potential source of serous carcinoma after prophylactic bilateral salpingo-oophorectomy. Because the gross and microscopic characteristics, as well as spread, of carcinoma of the fallopian tube are identical to those of the ovary, the determination of the site of origin of a tumor that forms a solid or cystic tubo-ovarian mass is arbitrary. The fallopian tube may actually be the source of many high-grade serous carcinomas that are considered as primary to the ovary.

Fallopian Tube Carcinoma

The gross appearance of the fallopian tube affected by papillary carcinoma is typically described as enlarged, deformed, or fusiform, with agglutination of the fimbriae and, frequently, distal obstruction. When the tumor is confined to the mucosa, the tube is generally soft to palpation, and the initial impression of the surgeon is often hematosalpinx, pyosalpinx, or hydrosalpinx. The most frequent site of origin is the ampulla, followed by the infundibulum. Microscopically, most fallopian tube neoplasms display papillary serous histology.

DIAGNOSIS AND CLINICAL EVALUATION

Ovarian carcinomas are distinctive by virtue of their propensity to exfoliate malignant cells into the peritoneal cavity. There the cells follow the normal circulation of peritoneal fluid up the right paracolic gutter and to the undersurface of the right hemidiaphragm, where they may implant and grow as surface nodules. The omentum is also a frequent site of involvement, and, indeed, all intraperitoneal surfaces are at risk. Ovarian cancer may also spread via the retroperitoneal lymphatics that drain the ovary. These follow the ovarian blood supply in the infundibulopelvic ligament to terminate in lymph nodes lying along the aorta and vena cava up to the

level of the renal vessels. Lymph channels also pass laterally through the broad ligament and parametrial channels to terminate in the pelvic sidewall lymphatics, including the external iliac, obturator, and hypogastric chains. Spread may also occur along the course of the round ligament, resulting in involvement of the inguinal lymphatics.

Approximately 75% to 85% of patients with epithelial ovarian cancer are diagnosed at the time when their disease has spread throughout the peritoneal cavity. Several organizations, including the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society, released a consensus statement on the symptoms of ovarian cancer in June 2007. It urges women to seek medical attention if they have new and persistent symptoms of bloating, pelvic or abdominal pain, difficulty eating, early satiety, or urinary urgency or frequency. These symptoms were found to be much more likely to occur in women with ovarian cancer than in the general population. There is, however, no evidence that detection based on these factors will shift diagnosis early enough to affect mortality.

The diagnosis of early-stage ovarian cancer (when the tumor is still confined to the pelvis) usually occurs by palpation of an asymptomatic adnexal mass during a routine pelvic examination. However, the vast majority of palpable adnexal masses are not malignant and, in premenopausal women, ovarian cancer represents less than 5% of adnexal neoplasms. In these women, the ovarian enlargement is usually due to either follicular or corpus luteum cysts. The vast majority of these functional cysts will regress in one to three menstrual cycles and, consequently, the initial approach to management for a palpable adnexal mass less than 8 cm in size in a premenopausal woman is to repeat the pelvic examination and imaging studies in 1 to 2 months. In contrast, an adnexal mass in a premenarchal or postmenopausal woman, particularly when complex as seen on ultrasound, has a higher likelihood of being a malignant tumor, and surgical exploration is usually indicated.

Preoperative evaluation of the ovarian cancer patient is shown in Figure 10.3. CT scans of chest, abdomen, and pelvis are usual. Brain scans and bone scans are unnecessary unless suggested by the patient's symptoms; metastases to these sites are extremely uncommon, particularly at the time of diagnosis. If there is concern for a gastrointestinal primary based on bowel symptoms or heme positive stools, barium enema or colonoscopy can be useful. Because of the association of ovarian cancer with breast cancer and because metastatic breast cancer can produce intra-abdominal carcinomatosis as well, mammography is often performed. Serum CA-125 level should be measured. It has been demonstrated that less than 1% of normal nonpregnant women have serum CA-125 levels greater than 35 U/mL. In contrast, 80% to 85% of patients with epithelial ovarian cancer have elevated serum levels. Unfortunately the percentage of women with an elevated CA-125 level is lower in stage I disease, limiting the usefulness of the marker as a screening test. The serous histologic subset of epithelial ovarian cancer has the highest incidence of elevated CA-125 levels (>85%), whereas mucinous tumors are associated with a low incidence of abnormally elevated serum CA-125 levels. In postmenopausal women with

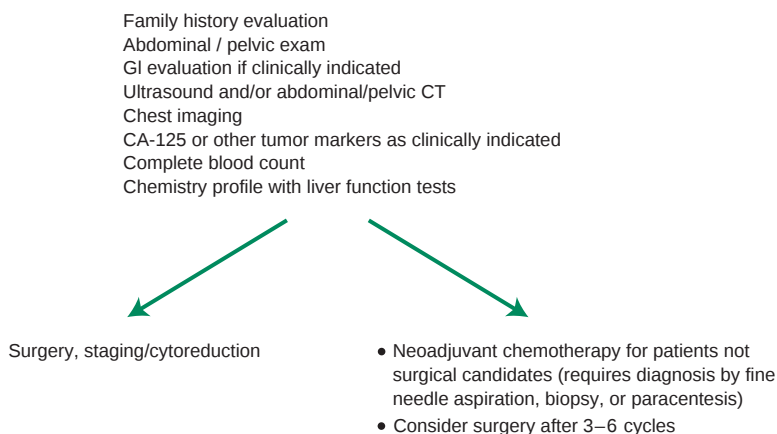


FIGURE 10.3. Suspicious symptoms/palpable mass or ascites.

asymptomatic pelvic masses, an elevated serum CA-125 (>65 U/mL) had a sensitivity of 97% and a specificity of 78% for ovarian cancer. In contrast, in premenopausal women, there is a higher prevalence of nonmalignant conditions that can produce elevated serum CA-125 levels (e.g., pregnancy, endometriosis, uterine fibroids, and pelvic inflammatory disease).

SCREENING

KEY POINTS

- Screening with pelvic exam, transvaginal ultrasound, and CA-125 has not been shown to be effective in any group of women, including BRCA mutation carriers.
- Premenopausal women frequently have palpable adnexal masses. Most are benign, and are due to follicular or corpus luteum cysts.
- Surgical exploration is generally indicated for adnexal masses in postmenopausal women.

Despite decades of large trials, no reliable procedures are currently available for the early detection of ovarian cancer. Available potential screening techniques have included pelvic examination (ovarian palpation), ultrasound examinations, CA-125 and other tumor markers, and combined modality approaches. Difficulties include the need for surgery, with its attendant risks, to evaluate a positive test and the fact that slow-growing tumors detected on screening are often borderline (which are not likely to be lethal) or already in an advanced-stage (which cannot usually be cured). A representative large multimodal screening trial, the NCI-sponsored Prostate,

Lung, Colorectal and Ovarian Cancer Screening Trial, enrolled over 74,000 women aged 55 to 74 from 1993 through 2000. Women were randomly assigned to either observation or baseline measurements of CA-125 levels and transvaginal ultrasonography followed by annual CA-125 readings for 5 years and transvaginal ultrasound for 3 years. Baseline screening in the 28,816 women randomized to screening who received at least one test detected 29 neoplasms (26 ovarian, 2 fallopian, and one primary peritoneal). Nine were of low malignant potential. Only two of the invasive cancers were stage I; one of these was a granulosa cell tumor. Five hundred seventy surgical procedures, including 325 laparotomies, were performed. The authors calculated the positive predictive value for invasive cancer of an abnormal CA-125 as 3.7%, of an abnormal transvaginal ultrasound as 1.0%, and of having both tests abnormal as 23.5%. However, if only subjects in whom both tests were abnormal had been evaluated, 12 of the 20 invasive cancers would have been missed.

Clearly it is possible that screening may do more harm (complications from needless procedures) than good. At this time, routine screening of the general population should not be performed. Even in women with a positive family history of ovarian cancer or known BRCA mutations, there is no evidence that screening can affect mortality from this disease. However, despite the lack of evidence for benefit of screening such high risk women, it seems prudent to follow them with pelvic and ultrasound examinations with serum CA-125 determinations on a regular basis until/unless they elect a prophylactic oophorectomy.

SURGICAL STAGING

KEY POINTS

- Surgical stage is the most important prognostic factor for women with ovarian carcinoma.
- Volume of residual disease after surgery is an important prognostic factor in women with advanced disease.
- Grade is a particularly important prognostic factor in women with early-stage disease.

The FIGO staging system for ovarian carcinomas is presented in Table 10.3. The stage usually can be determined only following exploratory laparotomy and thorough evaluation of all areas at risk. Operations on women with a pelvic or adnexal mass that may represent ovarian cancer should generally be carried out through a vertical abdominal incision to allow access to the upper abdomen, which is difficult to visualize through a low transverse incision. On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed to obtain specimens for cytologic examination. Separate specimens should be obtained from the pelvis, right and left paracolic gutters, and the undersurfaces of the right and left hemidiaphragms. An encapsulated adnexal mass should be removed intact, if

TABLE 10.3

CARCINOMA OF THE OVARY: FIGO NOMENCLATURE

Stage I	Growth limited to the ovaries.
IA	Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact.
IB	Growth limited to both ovaries; no ascites present containing malignant cells. No tumor on the external surfaces; capsules intact.
IC ^a	Tumor either stage IA or IB, but with tumor on surface of one or both ovaries, or with capsule rupture, or with ascites present containing malignant cells, or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.
IIA	Extension and/or metastases to the uterus and/or tubes.
IIB	Extension to other pelvic tissues.
IIC ^a	Tumor either Stage IIA or IIB, but with tumor on surface of one or both ovaries; or with capsule(s) rupture; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.
IIIA	Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery.
IIIB	Tumor of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, not exceeding 2 cm in diameter; nodes are negative.
IIIC	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

^aIn order to evaluate the impact of the different criteria on prognosis for allotting cases to stage IC or IIC, it would be of value to know if rupture of the capsule was spontaneous or caused by the surgeon, and if the source of malignant cells detected was peritoneal washings or ascites.

possible, since rupture and spillage of malignant cells within the peritoneal cavity will increase the patient's stage and may adversely affect her prognosis. Adhesions should be noted and biopsied since they may represent occult areas of microscopic disease. If frozen section indicates the presence of ovarian cancer, a complete abdominal exploration should be carried out, including the evaluation of all intestinal surfaces. Any suspicious areas should be biopsied. Omentectomy and random peritoneal biopsies should be performed. Aortic lymph node sampling should also be performed. Several reports have demonstrated that the pelvic lymph nodes are involved by ovarian cancer at the same frequency as are paraaortic nodes and suggest the need for routine pelvic node sampling as well.

Prognostic Factors

The 5-year survival of patients with epithelial ovarian cancer is directly correlated with the tumor stage (Fig. 10.4). Prognosis for stage I disease has been reported to be from 60% to over 80% and is strongly dependent on tumor grade and whether the patient was fully staged (as patients with apparent stage I disease may have stage III disease found with careful surgical exploration and node biopsy). Similarly, initial studies of patients with stage II disease reported the range of 5-year survivals from 0% to 40%. However, stage II disease frequently is upstaged to stage III disease, particularly when patients present with large-volume disease in the pelvis. The small number of patients who are found to have stage II disease following completion of a comprehensive laparotomy have a 5-year survival rate of approximately 80%. Patients with stage III disease have a 5-year survival

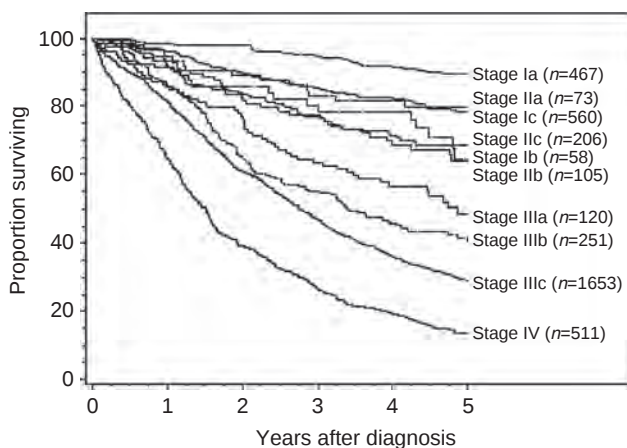


FIGURE 10.4. Carcinoma of the ovary; patients treated in 1996 to 1998. Survival of FIGO stage.

Source: Heintz AP, Odicino F, Maisonneve P, et al. Carcinoma of the ovary. *Int J Gynecol Obstet.* 2003;83:135–166.

rate of approximately 15% to 20%, whereas patients with stage IV disease have less than a 5% 5-year survival rate.

In women with advanced-stage disease, the volume of residual disease following cytoreductive surgery is directly correlated with survival. Patients who have been optimally cytoreduced have a 22-month improvement in median survival compared to those patients undergoing less than optimum resection.

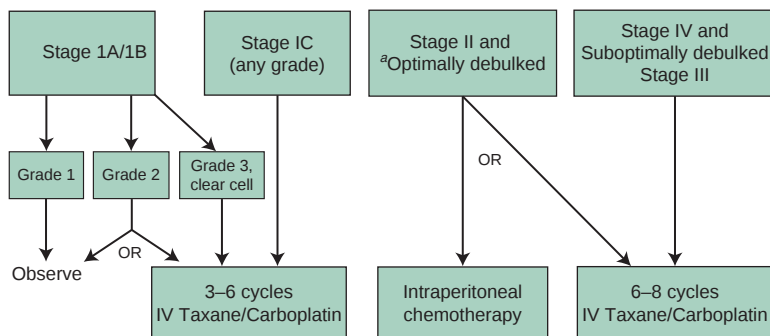
In general, the histologic type has less prognostic significance than the other clinical factors, such as stage, volume of disease, and histologic grade. However, there is a high correlation between histologic type, stage, and grade. The histologic grade of the tumor is a particularly important prognostic and decision-making factor in patients with early-stage ovarian cancer. In surgically staged patients from the International Federation of Gynecology and Obstetrics (FIGO) database, the overall 5-year survivals are 87%, 82%, and 69% for stage I grade 1, 2, and 3 tumors, respectively.

TREATMENT

A general algorithm for the management of ovarian cancer is seen in Figure 10.5.

Early-Stage Ovarian Cancer

Although the benefits of chemotherapy in advanced-stage ovarian cancer have been well demonstrated, they have been much harder to show in early-stage disease. The number of patients available is smaller and the prognosis better than with more advanced-stage disease, making adequately powered randomized trials difficult to complete. Some patients treated post-surgically only with observation may be salvaged with chemotherapy after recurrence. In addition, early-stage epithelial ovarian cancer is comprised



^aLess than 1 cm maximal size residual lesion

FIGURE 10.5. Postoperative chemotherapy.

TABLE 10.4

HISTOLOGY AND STAGE IN OVARIAN CANCER

	IA (n = 550)	IIIC (n = 1,793)
Serous	23%	67%
Mucinous	38%	7%
Endometrioid	19%	14%
Clear cell	10%	4%
Undifferentiated	3%	7%
Mixed	6%	2%

Source: Adapted from Heintz AP, Odicino F, Maisonneuve P, et al. *Int J Gynecol Obstet.* 2003;83(Suppl. 1):135–166.

of a rather different mix of grades and histologies than advanced-stage disease, in particular a much larger percentage of low-grade, mucinous, and clear cell carcinomas and a smaller percentage of serous carcinomas (Table 10.4). The current standard of care for most early-stage ovarian cancer is chemotherapy. This is based on the positive results of the combined ACTION and ICON-1 trials, which randomized women with early-stage disease to chemotherapy versus no postoperative treatment (Fig. 10.6). Duration of therapy for early-stage disease remains controversial. The GOG randomized 427 eligible patients with early-stage disease to receive either three or six cycles of carboplatin/paclitaxel chemotherapy. Overall 5-year survival was 84% for stage I disease and 73% for stage II disease, and did not differ by treatment regimen (HR 1.02). However, after adjusting for initial FIGO stage and tumor grade, the recurrence rate was 25% lower for patients getting six cycles (HR 0.761), and some physicians therefore prefer to use six cycles of chemotherapy.

At this time it is recommended that patients with comprehensively staged stage IA or IB grade 1 epithelial ovarian cancer receive no postoperative chemotherapy. Patients with grade 3 or stage IC disease have a relapse risk of at least 20%, and this can be reduced with platinum-based chemotherapy. Paclitaxel/carboplatin for three to six cycles is the usual treatment in the United States. It is hoped that future data will better address which women with early-stage ovarian cancers actually derive benefit from therapy.

Early-Stage Fallopian Tube Carcinomas

Unlike ovarian carcinoma, in which two thirds of patients present with advanced-stage disease, about half of patients diagnosed with fallopian tube carcinoma using traditional criteria have been diagnosed in stage I or II. Prognosis of early-stage disease has been reported to be dependent on depth of invasion of the tumor into the fallopian tube. Most recent data have suggested that

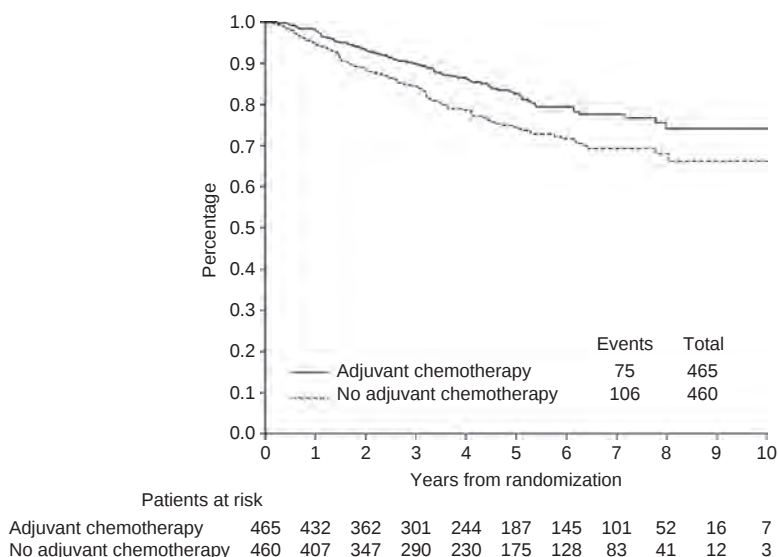


FIGURE 10.6. Kaplan-Meier curves for overall survival in early-stage ovarian cancer patients treated with adjuvant chemotherapy (*solid line*) and no adjuvant chemotherapy (*dotted line*).

Source: Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant Chemotherapy in Ovarian Neoplasm Trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. *J Natl Cancer Inst.* 2003;95:105–112.

the survival for women with fallopian tube cancer is similar or superior to that of women with ovarian cancer when standardized for stage. No meaningfully-sized series to inform about benefits of treatment exist. As advanced-stage fallopian tube carcinomas appear to respond to platinum-based therapies in a manner similar to that of ovarian carcinomas, adjuvant chemotherapy is currently used for early-stage fallopian tumor in most situations.

Management of Borderline Tumors

KEY POINTS

- Surgery is the primary management for borderline tumors.
- There is no evidence that postoperative chemotherapy improves outcomes for women with borderline ovarian cancer even with advanced-stage disease.
- Borderline tumors may recur after 10 to 15 years.

Borderline tumors comprise 10% to 20% of ovarian malignancies. Most are of serous or mucinous histology and most are diagnosed at an early stage.

Even when they present with more advanced-stage disease, they progress very slowly. A review of borderline tumors entered into the NCI SEER database between 1988 and 1997 showed 10-year relative survivals of 99% for stage I, 98% for stage II, 96% for stage III, and 77% for stage IV disease. Borderline tumors are particularly likely to affect young women (Fig. 10.1), in whom therapeutic decisions regarding fertility-sparing, premature hormonal deprivation, and adjuvant chemotherapeutic treatments are particularly pertinent.

Surgery is the cornerstone of treatment for early-stage as well as advanced-stage ovarian borderline tumors. There is no evidence that a conservative surgical approach has an adverse effect on survival in patients with stage I borderline tumors. Even though patients treated with a unilateral oophorectomy have a higher recurrence rate than patients treated with a total hysterectomy and bilateral oophorectomy, effective surgery for recurrent disease leads to equivalent survival. Chemotherapy is not indicated for stage I or II borderline tumors.

Approximately 5% to 10% of early-stage serous borderline tumors will ultimately recur, either as borderline tumors or low-grade carcinomas. Recurrences can present 10 to 15 years after the initial diagnosis, making long-term follow-up necessary. Although their very slow growth would seem to predispose them to resistance to traditional cytotoxic agents, serous borderline tumors are not completely chemotherapy-resistant, and response rates of 15% to 57% to front-line therapy have been reported. Surgery is often used as sole primary treatment for women with serous borderline tumor of the ovary with noninvasive implants, for whom 5-year survivals are 94% to 95%, and chemotherapy is often used in women with invasive implants. However, there is no clear evidence that chemotherapy can decrease relapse rates or improve survival in any subset of patients. Over 90% of serous borderline ovarian tumors are estrogen-receptor positive, and there are case reports of major responses to tamoxifen, leuprolide, and anastrozole.

Most mucinous borderline ovarian tumors are stage I and present as large unilateral ovarian masses; bilaterality suggests the possibility of metastatic tumor from another site. Appendectomy and evaluation of the GI tract should be performed to rule out a primary gastrointestinal tumor. Advanced-stage pure borderline mucinous tumors are exceedingly uncommon.

Advanced Epithelial Ovarian Cancer

KEY POINTS

- Cytoreductive surgery is standard in the management of ovarian cancer.
- Six cycles of carboplatin/paclitaxel represents standard therapy for most women with advanced-stage ovarian cancer in the United States.
- There is no confirmed survival benefit for platinum dose escalation, any maintenance therapy, or addition of a third cytotoxic agent.
- Intraperitoneal therapy may benefit women with small volume disease.
- Advanced-stage clear cell and mucinous tumors appear to be relatively chemotherapy-resistant.

Cytoreductive Surgery

The majority of cases of cancer of the ovary are not diagnosed until the disease has spread beyond the ovary. Often, patients with advanced disease will present with an abdomen distended with ascites and obviously bulky tumor masses in the pelvis and upper abdomen. Removal of bulky tumor masses in a patient with advanced ovarian cancer may improve the patient's comfort, reduce the adverse metabolic consequences of the tumor, and enhance the patient's ability to maintain her nutritional status. Removal of large tumor masses may also enhance the response of the remaining tumor to chemotherapy. Large tumor masses with a relatively poor blood supply may provide a pharmacologic sanctuary where viable tumor cells can escape exposure to adequate concentrations of cytotoxic drugs. Additionally, such poorly vascularized masses may have a low growth fraction (i.e., a larger proportion of cells in the nonproliferating [G_0] phase of the cell cycle) when they are relatively insensitive to the effects of cytotoxic drugs. In clinical trials in which the percentage of patients who were optimally cytoreduced was reported, the median survival for optimally cytoreduced patients (i.e., those with a maximum remaining lesion size of less than a centimeter) was 39 months as compared to 17 months for those not optimally cytoreduced. However, randomized clinical trial data supporting aggressive debulking surgery do not exist. It is possible that patients who present with small-volume disease have disease that is biologically less aggressive than do patients who are anatomically cytoreduced to the same amount of residual disease after surgical removal of bulky tumor.

Surgery prior to chemotherapy, for diagnosis and tumor debulking, has been the standard in the United States. However, since many patients cannot be successfully cytoreduced at initial surgery, the benefit of a brief induction course of chemotherapy prior to debulking surgery has been explored. Two to three cycles of chemotherapy substantially increase the percentage of patients who will be successfully cytoreduced and decrease operative morbidity. This approach clearly seems appropriate in patients who are poor surgical candidates at presentation. Whether it should be more universally applied remains controversial.

Interval debulking is a term traditionally used to describe surgery performed in the middle of a chemotherapy course for patients in whom initial debulking surgery was attempted, but was unsuccessful, and whose disease appears to be responding to therapy. There is conflicting evidence from two large prospective randomized trials (EORTC and GOG) as to whether interval debulking can improve survival in certain patients with advanced ovarian cancer, with an EORTC trial showing substantial benefit and a GOG trial showing no benefit in either progression-free or overall survival. It has been hypothesized that the differences in outcome result from a more aggressive initial surgical attempt in the United States. Selected patients may benefit from interval debulking depending on the aggressiveness of the initial cytoreductive surgery, the geographic distribution and size of the remaining disease, and the response to the initial several cycles of chemotherapy.

Chemotherapy

Surgery is rarely curative for women with advanced-stage ovarian carcinoma, even when there is no residual disease. The most standard regimen in the United States is currently six cycles of postoperative intravenous paclitaxel/carboplatin; areas of uncertainty exist not only regarding the use of neoadjuvant therapy and interval debulking, but regarding the role of single-agent carboplatin, use of intraperitoneal chemotherapy, and use of maintenance therapy.

Platinum Use

Platinum agents represent the most active group of chemotherapy drugs in the treatment of ovarian cancer. Multiple randomized trials comparing carboplatin to cisplatin in ovarian carcinoma have been performed, and both individual studies and meta-analyses have confirmed that there is no difference in efficacy between the two agents. No evidence supports the use of doses of cisplatin above 50 to 100 mg/m² every 3 weeks or carboplatin AUC 5 to 7.5 every 3 weeks. Oxaliplatin also has activity against ovarian cancer, but has not been shown to be superior to, noncross resistant with, or less toxic than carboplatin. Therefore, in general, carboplatin, which is less emetogenic and produces less neurotoxicity and nephrotoxicity than cisplatin, is the first-line platinum agent in the treatment of ovarian cancer in the United States. However, as discussed below, there are no randomized data showing that intraperitoneal carboplatin produces benefits similar to those seen with intraperitoneal cisplatin, and cisplatin remains the standard platinum drug for intraperitoneal administration.

Addition of a Taxane to Platinum Chemotherapy

In the 1980s, a great deal of excitement was generated by the demonstration that single agent paclitaxel had substantial activity against platinum-resistant ovarian cancer.

A number of randomized trials were rapidly launched comparing platinum-based regimens with and without taxane in the first-line treatment of ovarian cancer. The four largest studies are summarized in Table 10.5. The results of the first two of these trials completed (GOG-111 and OV-10) clearly demonstrated that combination chemotherapy with paclitaxel and cisplatin prolongs both progression-free and overall survival as compared with cyclophosphamide/cisplatin. However, the other two trials did not clearly support the addition of paclitaxel to front-line therapy. GOG-132 compared single agent paclitaxel to single agent cisplatin to the combination of cisplatin and paclitaxel. The response rate to single agent paclitaxel in patients with measurable disease was significantly lower than to either of the platinum-containing regimens (42% vs. 67%, $p < 0.01$). However, there was no difference in overall survival (30.2, 25.9, and 26.3 months) between the regimens. It is possible that sequential therapy with platinum and taxane would produce the same results as combined therapy, but this has not been prospectively demonstrated, and combination platinum/taxane therapy remains the standard in the United States.

TABLE 10.5

RANDOMIZED TRIALS ± TAXANE IN FIRST LINE CHEMOTHERAPY FOR OVARIAN CANCER

Author (year)	N	Eligibility	Regimens	Median PFS	Median OS
McGuire (1996) GOG-111	386	Suboptimal III any IV	Cisplatin 75 mg/m ² + Paclitaxel 13.5 mg/m ² /24 hr vs. Cisplatin 75 mg/m ² + Cyclophosphamide 750 mg/m ²	18 months vs. 13 months <i>p</i> < 0.001	38 months vs. 24 months <i>p</i> < 0.001
Piccart (2000) OV-10	680	IIIb-IV	Cisplatin 75 mg/m ² + Paclitaxel 175 mg/m ² /3 hr vs. Cisplatin 75 mg/m ² + Cyclophosphamide 750 mg/m ²	15.5 months vs. 11.5 months <i>p</i> = 0.0005	35.6 months vs. 25.8 months <i>p</i> = 0.0016
Muggia (2000) GOG-132	614	Suboptimal III any IV	Cisplatin 75 mg/m ² + Paclitaxel 135 g/m ² /24 hr vs. Paclitaxel 200 mg/m ² /24 hr vs. Cisplatin 100 mg/m ²	14 months vs. 11 months vs. 16 months Paclitaxel worse <i>p</i> < 0.001	26 months vs. 26 months vs. 30 months <i>p</i> = NS
ICON-3 (2002)	2,075	I-IV	Carboplatin AUC 6 + Paclitaxel 175 mg/m ² vs. Carboplatin AUC 6 or CAP (<i>n</i> = 421) Cyclophosphamide 500 mg/m ² + Cisplatin 50 mg/m ² + Doxorubicin 50 mg/m ²	17 months vs. 16 months <i>p</i> = NS	39 months vs. 36 months <i>p</i> = NS

Alternate Taxanes/Taxane Schedules

Docetaxel plus carboplatin has been prospectively compared to paclitaxel plus carboplatin. There were no apparent differences in progression-free or overall survival between the two drugs. Docetaxel was associated with less neurotoxicity but more myelotoxicity. It represents an attractive option for patients with or at risk for neurotoxicity. Higher doses or more prolonged infusions of paclitaxel have not been shown to be of benefit. However, phase II trials of weekly paclitaxel have reported response rates of 32% to 47% in platinum-refractory patients, and there is substantial interest in the incorporation of weekly paclitaxel into front-line therapy of ovarian cancer. Preliminary results from a trial conducted in Japan comparing weekly paclitaxel plus every-3-week carboplatin to every-3-week paclitaxel plus every-3-week carboplatin have suggested superior outcomes but increased toxicity with the weekly paclitaxel schedule.

Addition of a Third Agent to Front-line Chemotherapy

There are no data to prove that the addition of any third cytotoxic agent to front-line chemotherapy of ovarian cancer improves outcomes. An international multiarm randomized study was led by the GOG (GOG-182 –ICON-5) to definitively answer whether triplet cytotoxic chemotherapy improves survival. A total of 4,312 advanced-staged ovarian cancer patients were randomized to carboplatin/paclitaxel or carboplatin/paclitaxel combined with gemcitabine, liposomal doxorubicin, or topotecan. Progression-free survival was not statistically different among any of the combination regimens studied.

Recent interest has focused on the role of combining some of the newer molecular targeted agents with chemotherapy. The most promising agent to date has been with bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF). It has produced single agent response rates in the range of 20% in the setting of recurrent ovarian cancer, and has improved survival when combined with chemotherapy in the treatment of metastatic colon cancer and lung cancer. Two large randomized trials testing the addition of bevacizumab to front-line therapy (GOG-218 and ICON-7) have recently been completed, and results should be available soon.

Intraperitoneal Chemotherapy

Intraperitoneal (IP) chemotherapy provides a means by which high concentrations of drugs and long durations of tissue exposure can be attained at the peritoneal surface. As intraperitoneal progression of disease remains the major source of morbidity and mortality in ovarian cancer, it is a theoretically attractive approach in the treatment of this disease. It should be noted that (i) the theoretical benefit is only for very small tumor volumes and (ii) agents that do not reach therapeutic systemic levels when given by the intraperitoneal route need to be administered intravenously as well. For a given dose of cisplatin, peak concentrations are higher with IV cisplatin, and this has resulted in somewhat decreased toxicity in a randomized

comparison of the same doses of cisplatin given intraperitoneally versus intravenously, including less hearing loss and neuromuscular toxicity. However, the amount of cisplatin recovered in the urine, reflecting total systemic exposure, is similar regardless of whether the administration is intravenous or intraperitoneal. Similarly, carboplatin given IP at an AUC of six has been shown to give an AUC in the peritoneal cavity of about 17 times higher than that of carboplatin given intravenously while producing a very similar serum AUC. For paclitaxel, on the other hand, serum concentrations in patients treated with intraperitoneal paclitaxel at feasible doses are low. However, significant levels persist in the peritoneal cavity one week after drug administration.

Clinical Use of IP Therapy for Ovarian Cancer

Numerous prospective randomized clinical trials have tested the benefit of intraperitoneal cisplatin in the treatment of ovarian cancer; the three largest are summarized in Table 10.6. In January 2006, the NCI issued a clinical alert suggesting the use of intraperitoneal cisplatin chemotherapy in women with optimally debulked ovarian cancer. A meta-analysis of eight trials comparing intraperitoneal to intravenous platinum-based chemotherapy (all but one used cisplatin) showed an average 21.6% decrease in the risk of death ($HR = 0.79$). As the expected median duration of survival for women with optimally debulked ovarian cancer receiving standard treatment is approximately 4 years, this size reduction in death rate was estimated to translate into about a 12-month increase in overall median survival. Despite these results, intraperitoneal therapy has not yet been consistently adopted for the treatment of women with optimally debulked ovarian cancer in the United States, and has not been widely adopted internationally. There are several reasons for this. First, intraperitoneal therapy, as used in the reported trials, is technically demanding. Administration of paclitaxel over 24 hours, which has been used to reduce the neurotoxicity when paclitaxel is combined with cisplatin, is inconvenient and, if it requires hospitalization, expensive. Use of IP catheters is not routine in many oncology practices, and is associated with a number of complications including intestinal injury, catheter blockage, and infections. Second, all of the large randomized studies used cisplatin in both the intraperitoneal and intravenous arms, whereas carboplatin, which is less toxic and easier to administer, has become the standard intravenous platinum agent in the treatment of ovarian cancer. While intraperitoneal carboplatin can be safely used and appears to have favorable pharmacokinetics (pharmacologic advantage combined with good systemic drug exposure), there is no clinical trial evidence that it will provide the same survival benefits as intraperitoneal cisplatin. Finally, the heterogeneity and toxicity of the intraperitoneal regimens used have left some confusion as to what the most important elements of the ideal IP therapy regimen are, and which could be modified to improve safety and tolerability while maintaining efficacy. For example, the Markman trial used two cycles of carboplatin AUC 9 (as “chemical debulking” prior to starting intraperitoneal therapy), which resulted in significant hematologic toxicity and

TABLE 10.6
SELECTED RANDOMIZED TRIALS OF INTRAPERITONEAL VERSUS INTRAVENOUS
CHEMOTHERAPY IN OPTIMALLY DEBULKED OVARIAN CANCERS

Author (year)	N	Regimens	Median PFS	Median OS	Comments
Alberts (1996)	546	IV cyclophosphamide 600 mg/m ² + IP cisplatin 100 mg/m ² × 6	N/A	49 months vs. 41 months <i>p</i> = 0.02	<2 cm residual disease permitted; 58% of patients in both groups completed six cycles of cisplatin
		IV cyclophosphamide 600 mg/m ² + IV cisplatin 100 mg/m ² × 6			
Markman (2001)	462	IV carboplatin AUC 9 × 2 followed by IV paclitaxel 135 mg/m ² /24 hr + IP cisplatin 100 mg/m ² × 6	28 months vs. 22 months <i>p</i> = 0.01	63 months vs. 52 months <i>p</i> = 0.05	18% of patients on IP arm got ≤ 2 cycles of IP therapy
		IV paclitaxel 135 mg/m ² /24 hr + IV cisplatin 75 mg/m ² × 6			
Armstrong (2006)	416	DI IV paclitaxel 135 mg/m ² /24 hr + D2 IP cisplatin 100 mg/m ² + D8 IP paclitaxel 60 mg/m ²	24 months vs. 19 months <i>p</i> = 0.027	67 months vs. 50 months <i>p</i> = 0.0076	49% of patients received ≤ 3 cycles of IP therapy
		D1 IV paclitaxel 135 mg/m ² /24 hr + D2 IV cisplatin 75 mg/m ²			

difficulty delivering the IP regimen. The Armstrong trial incorporated both IP cisplatin and IP paclitaxel. Despite these uncertainties, a potential 1-year survival advantage is certainly meaningful, and the option of intraperitoneal therapy should be discussed with healthy patients who have optimally debulked ovarian cancer. Ongoing trials will clarify the benefit of simplified, less toxic regimens.

Prolongation of Primary Therapy/Consolidation/Maintenance

Many women with ovarian cancer have an excellent response to first-line chemotherapy, but most will nonetheless relapse and die of their disease. Further therapy after a clinical complete remission would clearly be warranted for many women if an effective treatment could be found. Strategies tested in randomized trials include whole abdominal radiotherapy, intraperitoneal P32, intraperitoneal cisplatin, greater than six cycles of primary therapy, consolidation with a different agent such as topotecan or epirubicin, and high-dose chemotherapy with stem cell support. However none of these approaches have produced any convincing survival benefit to date.

The most promising trial of maintenance therapy to date has been a SWOG/GOG trial randomizing women in clinical complete remission to either 3 or 12 cycles of intravenous paclitaxel 175 mg/m² every 4 weeks. The trial was halted by its data and safety monitoring board after a planned interim efficacy analysis at a point when there was a statistically significant improvement in time to progression (PFS 28 vs. 21 months) but no difference in overall survival between the treatment arms. A preliminary report on results of an Italian trial randomizing women in complete remission after front-line therapy to observation or six cycles of paclitaxel 175 mg/m² every 3 weeks showed no benefit in either progression-free or overall survival. The GOG is attempting to confirm the beneficial results it observed with a larger study randomizing women after clinical complete remission to one of three arms: no further therapy, paclitaxel 135 mg/m² every 4 weeks for 12 cycles, or xyotax (a microparticle-bound paclitaxel) 135 mg/m² every 4 weeks for 12 cycles. This trial currently has overall survival as the endpoint. In addition, maintenance bevacizumab is being tested as part of the GOG-218 trial testing the benefit of bevacizumab in front-line therapy.

Current treatment recommendations for women with advanced-stage fallopian tube carcinoma or primary peritoneal serous carcinomas are the same as for women with advanced-stage ovarian carcinomas.

Implications of Clear Cell and Mucinous Histology

Advanced clear cell carcinomas are unusual in the United States. Clear cell carcinoma is more common in Japan, where it accounts for about 20% of epithelial ovarian carcinomas. Even in Japan, early-stage clear cell carcinoma is more common than advanced-stage disease; in one review, stage I made up 39% of clear cell disease, stage II 13%, stage III 30%, and stage IV 6%. The implications of clear cell histology in early disease are not clear;

in some reports it seems to portend a high risk of recurrence, and in others it appears to have little prognostic significance. However it has become increasingly clear that advanced-stage clear cell tumors may not respond well to platinum chemotherapy. For example, the Hellenic Cooperative Oncology Group reviewed outcomes for women with an advanced clear cell carcinoma of the ovary treated on protocols from 1987 and 2003 ($n = 35$), and compared them to outcomes for women with serous tumors treated on the same trials. Response rates were 45% versus 81% ($p = 0.008$) and median survival was 25.1 months versus 49.1 months ($p = 0.141$). Clinical data regarding differential chemotherapy sensitivity to various agents of clear cell carcinomas are sparse and inconsistent. A multinational phase III study for stage I to IV clear cell carcinomas of the ovary has been launched by the Japanese Gynecologic Oncology Group. Women are randomized to therapy with either carboplatin/paclitaxel or cisplatin/irinotecan. It has also been hypothesized that antiangiogenic agents will benefit women with clear cell carcinomas, but this remains unproven. Interestingly, multiple reports suggest that women with clear cell carcinomas are more likely to have a thromboembolic event. Clear cell carcinomas may also be associated with hypercalcemia.

Early-stage mucinous tumors tend to be low-grade and have a good prognosis. Advanced-stage mucinous tumors are uncommon in the United States, and are difficult to distinguish from mucinous tumors metastatic from other sites. They respond poorly to chemotherapy and are associated with a short survival. Investigators from the Royal Marsden Hospital reviewed all patients with stage III or IV mucinous epithelial ovarian cancer ($n = 27$, 19 with measurable disease) treated with first line platinum-based therapy at their unit between 1992 and 2001 and compared them to controls with nonmucinous epithelial ovarian cancer. The response rate for patients with measurable mucinous cancer was only 26%; 63% of patients experienced disease progression while on platinum-based chemotherapy. The response rate for the controls with measurable disease was 65%. Median overall survival was 12 months versus 37 months ($p < 0.001$). Specific trials are being developed for patients with advanced-stage mucinous tumors.

Second-Look Surgery

The term *second-look laparotomy/laparoscopy* refers to an abdominal procedure after chemotherapy to assess whether or not residual disease remains. At least half of patients in clinical complete remission with a normal CA-125 level will have residual disease at laparotomy. Second-look procedures used to be routine, and provided important information about the natural history of ovarian cancer. However, although surgery is the most accurate way to assess the response to therapy, there is no evidence that any type of routine surgical procedure after initial chemotherapy prolongs overall survival or that any further therapy administered

to patients with clinically inapparent residual disease will prolong survival. Moreover, even patients with negative second-look laparotomy have a 50% recurrence risk. This type of procedure is therefore no longer current standard of practice.

Follow-up of Patients in Remission

Because of the high relapse risk, most patients with ovarian cancer who enter a clinical complete remission have been followed with a combination of pelvic examinations, computerized abdominal tomograms, and monitoring of serum CA-125 levels. However, none of these have been shown to decrease symptoms or improve survival. Unlike the situation in general screening, rise in CA-125 after primary treatment for ovarian cancer is fairly specific, particularly if a confirmatory test is obtained. However, a randomized trial testing initiation of chemotherapy at the time of CA-125 rise versus at the time of clinical recurrence did not show any benefit in terms of survival or quality of life.

TREATMENT OF PERSISTENT/ RECURRENT DISEASE

KEY POINTS

- Recurrent ovarian cancer is generally incurable, but patients who recur more than 6 months after completion of primary therapy may have significant benefit from further chemotherapy.
- Combination therapy produces higher response rates than single agent chemotherapy in women with platinum-sensitive disease, but data regarding any overall survival benefit are conflicting.
- The value of secondary debulking surgery is being tested in the clinical trial setting.

Second-Line Chemotherapy

Ovarian cancer that is resistant to primary chemotherapy or recurs at some point after primary chemotherapy is generally not curable. However some patients benefit from further treatment, in particular those who relapse after a substantial disease-free interval. The GOG defines ovarian cancers with progression on platinum-based therapy as “platinum-refractory,” those which recur less than 6 months after completion of platinum-based therapy as “platinum-resistant,” and those which recur more than 6 months after completing treatment with a platinum-based regimen as “platinum sensitive” (short for “potentially platinum sensitive”). Women with primary platinum-refractory therapy have a very poor prognosis, and response to any subsequent

treatment is unlikely. General principles of treating recurrent disease include the following:

1. Although platinum-sensitive tumors are more sensitive than platinum-resistant tumors to any cytotoxic agent tested to date, most data suggest that platinum compounds are the most active single agents in women with platinum-sensitive recurrent disease.
2. Platinum-based combinations of cytotoxic agents produce superior response rates and progression-free survival compared with single agent platinum therapy in women with platinum-sensitive disease; the effect on overall survival is less certain, and toxicity may be increased. In women with platinum-resistant disease, combination therapy has never been shown to provide any benefit.
3. No agents except possibly taxanes have consistently produced response rates over 20% in women with platinum-resistant disease.
4. Treatment must be recognized as primarily palliative, and decisions about treatment regimens should include patient convenience and toxicity as well as efficacy.

Platinum-Sensitive Disease

Several randomized trials comparing platinum-containing combinations including paclitaxel, gemcitabine, and liposomal doxorubicin to single agent platinum therapy produce superior progression-free survival to single agent platinum therapy in the setting of platinum-sensitive disease. As a group, they show a superior response rate and superior progression-free survival with combination therapy. Results regarding any benefit to overall survival are conflicting, and any such benefit is probably small. Secondary debulking surgery has been hypothesized to be of benefit in this group, and a randomized trial testing this approach is underway.

Repeated courses of carboplatin-based therapy place patients at risk for hypersensitivity reactions. The incidence in patients treated with seven or more cycles of platinum-based therapy (typically the second dose of the second regimen) has been reported to be 27%. These reactions that occur during drug infusion are associated with flushing, nausea, and hypertension. A number of desensitization protocols have been published and appear to be generally effective; moreover, not all patients allergic to carboplatin will be allergic to cisplatin. However, the reactions are frightening and may be fatal and desensitization protocols are time-consuming for the patient and decrease the convenience of carboplatin therapy. Routine use of diphenhydramine premedication has been reported to produce a non-significant decrease in reaction rate.

Treatment of Platinum-Resistant Disease

Response rates to any conventional single agent therapy in this group of women are about 10% to 20%; median progression-free survival is about 3 to 4 months, and median overall survival is 9 to 12 months. A list of agents with some activity in the treatment of platinum-resistant recurrent ovarian cancer is shown in Table 10.7. At this time, pegylated liposomal

TABLE 10.7

AGENTS IN TREATMENT OF PLATINUM-RESISTANT
OVARIAN CANCER

Bevacizumab
Docetaxel
Epirubicin
p.o. Etoposide
Gemcitabine
Ifosfamide
Tamoxifen
Weekly paclitaxel
Topotecan
Vinorelbine
Pegylated liposomal doxorubicin
Irinotecan

doxorubicin is one of the agents commonly used in this setting, based on the ease of administration and tolerable toxicity.

Hormonal therapies, such as tamoxifen, and antiangiogenics, such as bevacizumab, have also been tested. Response rates to hormonal treatment by modern standards are hard to gauge, as most of the trials are quite old; however, it does appear that selected patients, perhaps those with borderline tumors, may respond and toxicities are minimal. Antiangiogenics appear promising in the treatment of ovarian cancer. None, including bevacizumab, an anti-VEGF monoclonal antibody that has produced single agent response rates in the range 15% to 20% in the treatment of ovarian cancer, are currently FDA approved for the treatment of ovarian cancer. All are exceedingly expensive, and bevacizumab has been associated with a number of toxicities, including an increased number of bowel perforations.

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CHAPTER 11 ■ NONEPITHELIAL OVARIAN CANCER

PATHOLOGY

KEY POINTS

- The most common malignant germ cell tumors in females are (i) dysgerminomas, (ii) endodermal sinus tumors, and (iii) immature teratomas (ITs).
- Grade is important only for ITs.

The current World Health Organization classification of ovarian germ cell tumors includes dysgerminoma, yolk sac tumor (endodermal sinus tumors), embryonal carcinoma, polyembryoma, nongestational choriocarcinoma, mixed germ cell tumors, and teratomas (immature, mature, and monodermal types).

Dysgerminoma

Dysgerminoma represents the most common ovarian malignant germ cell tumor. It is the most frequent ovarian neoplasm in patients with gonadal dysgenesis. However, most dysgerminomas occur in normal females who usually present with abdominal enlargement, a mass, or pain due to torsion. About 10% of dysgerminomas are bilateral on gross examination and another 10% have microscopic involvement of the contralateral ovary.

On gross examination, dysgerminomas are usually large, white to gray, fleshy lobulated masses. Abundant hemorrhage, necrosis, or cystic areas in a well-fixed tumor should raise the question of a mixed germ cell tumor. Microscopically, dysgerminomas display nests and cords of primitive appearing germ cells with clear to eosinophilic cytoplasm and prominent cytoplasmic borders. Mitoses may be numerous, but the number of mitotic figures does not have any therapeutic or prognostic significance.

Dysgerminomas contain cytoplasmic glycogen that can be demonstrated with a periodic acid-Schiff stain and display diffuse staining for placenta-like alkaline phosphatase (PLAP). Positive staining of dysgerminomas for c-kit and the nuclear transcription factor OCT 3/4 are helpful in confirming this diagnosis. Dysgerminoma is the only ovarian germ cell tumor that displays c-kit staining. Both dysgerminoma and embryonal carcinoma stain for OCT 3/4. In contrast to embryonal carcinoma, dysgerminoma does not stain for CD30. Syncytiotrophoblast cells present in dysgerminomas display human chorionic gonadotropin (hCG) staining.

Dysgerminomas do not produce alpha fetoprotein (AFP), a finding that may be helpful in distinguishing them from the solid variant of yolk sac tumor. Poor fixation can result in artifacts that mimic embryonal carcinoma and yolk sac tumor histology.

Yolk Sac Tumor

Yolk sac tumor (endodermal sinus tumor) is the second most common ovarian germ cell tumor. These tumors grow very rapidly, often becoming clinically evident in less than 1 month.

Yolk sac tumors are typically large and unilateral, with a smooth external surface. On cut section, these neoplasms are tan to gray, with abundant hemorrhage and necrosis. They may be partially solid, but they usually contain cysts that vary in size from a few millimeters to several centimeters in diameter. The cut surface appears mucoid, slimy, or gelatinous. Yolk sac tumors display many different histologic patterns. The most common is the reticular or microcystic pattern. The tumor has a meshlike pattern and it displays a network of flattened or cuboidal epithelial cells with varying degrees of atypia. The endodermal sinus (festoon) pattern contains Schiller-Duval bodies (Fig. 11.1) that have a central capillary surrounded by connective tissue and a peripheral layer of columnar cells. These structures are situated in cavities lined by yolk sac tumor cells. When present, Schiller-Duval bodies are diagnostic of yolk sac tumor. Yolk sac tumors generally, though not always, display cytoplasmic staining for cytokeratin and AFP.

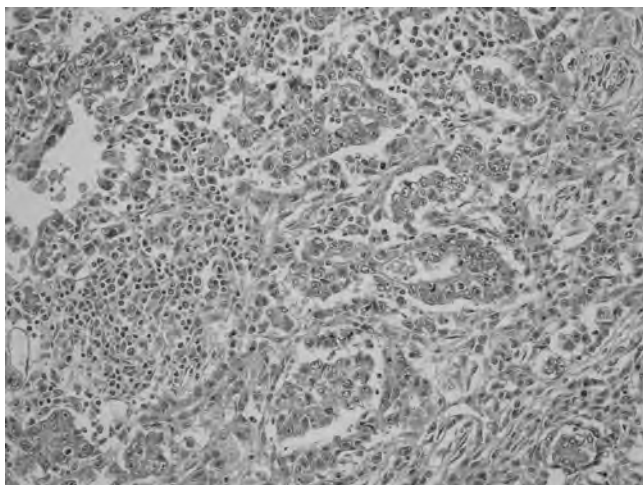


FIGURE 11.1. Schiller-Duval bodies, papillary structures with central blood vessels, are seen in the endodermal sinus pattern of yolk sac tumor.

Embryonal Carcinoma

Embryonal carcinoma is rarely seen in the ovary, in contrast to its frequent occurrence in the testis. Only 14 cases were identified during a period of 30 years at the Armed Forces Institute of Pathology, and there have been no recent large series of these tumors. On gross examination, embryonal carcinoma characteristically displays areas of hemorrhage and necrosis. Microscopically, this tumor is composed of very crowded cells that display overlapping nuclei in paraffin sections. The nuclei are very pleomorphic and they contain large, prominent nucleoli. The mitotic rate is high in these tumors. Glandular, solid, and papillary patterns may be seen. Vascular invasion is common. Embryonal carcinoma stains positively for PLAP, pancytokeratin (AE1/AE3 and CAM 5.2), CD30, and OCT3/4. In contrast to seminoma, embryonal carcinoma does not display c-kit staining. Some embryonal carcinomas display focal AFP positivity that may represent partial transformation to yolk sac tumor. Syncytiotrophoblast cells may be present. They produce hCG, but they are not accompanied by admixed cytotrophoblast cells unless choriocarcinoma is also present.

Polyembryoma

Polyembryoma is a very rare malignant ovarian tumor. In the few cases reported, the embryoid bodies characteristic of this germ cell tumor have coexisted with other germ cell tumor types. The microscopic appearance of embryoid bodies with an embryonic disc separating a yolk sac and an amniotic cavity may actually be due to an admixture of yolk sac tumor and embryonal carcinoma.

Choriocarcinoma

Primary nongestational ovarian choriocarcinoma is rare. It is most often seen as a component of mixed germ cell tumors of the ovary. Choriocarcinomas display abundant hemorrhage and necrosis on gross examination. Microscopically, these neoplasms show a plexiform pattern composed of an admixture of syncytiotrophoblast and cytotrophoblast cells. Numerous mitoses are present. Choriocarcinoma spreads by blood vessel invasion that is easy to identify in these tumors. Cytotrophoblast cells do not produce hCG. Syncytiotrophoblast cells are formed from cytotrophoblast cells, and do produce hCG. Choriocarcinoma may also stain for cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen. Nongestational choriocarcinoma must be distinguished from gestational choriocarcinoma because the former has a worse prognosis and requires more aggressive therapy. The identification of paternal genetic material indicates that the tumor is of gestational origin.

Mixed Germ Cell Tumors

Mixed germ cell tumors of the ovary contain two or more different types of germ cell neoplasm, either intimately admixed or as separate foci within

the tumor. They are much less common in the ovary than in the testis, accounting for only about 8% of malignant ovarian germ cell tumors.

The diagnosis and prognosis of malignant mixed germ cell tumors depend on adequate tumor sampling in order to detect small areas of different types of germ cell tumor because the types of tumor identified may affect therapy and prognosis.

Teratomas

Teratomas are germ cell tumors that contain tissue derived from two or three embryonic layers. Teratomas are subclassified according to whether the tumor elements represent mature or immature tissue types. In addition, some teratomas are composed of a predominance of one tissue type such as thyroid tissue (struma ovarii). In contrast to other ovarian germ cell tumor types, ovarian teratomas do not contain 12p amplification.

Most teratomas are mature cystic teratomas that contain differentiated tissue components such as skin, cartilage, glia, glandular elements, and bone. Any tissue type present in adults may be represented in teratomas. Mature cystic teratomas represent benign neoplasms unless they contain a somatic malignancy such as squamous carcinoma, papillary thyroid carcinoma or other non-germ cell tumors arising in differentiated elements of the teratoma.

Immature teratomas (ITs) in adult women, in contrast to mature cystic teratomas, are uncommon tumors. They represent only about 3% of all ovarian teratomas, but ITs are the third most common form of malignant ovarian germ cell tumors. Very limited amounts of immature tissue occurring in mature cystic teratomas does not seem to alter the prognosis of those tumors, but immature tissue in solid teratomas represents a malignant tumor that can disseminate and metastasize.

Most immature ovarian teratomas are unilateral, although they can metastasize to the opposite ovary and can also be associated with mature teratoma in the opposite ovary. They are predominantly solid tumors, but they may contain some cystic areas. The cut surface of an IT is soft and fleshy in appearance. Areas of hemorrhage and necrosis are common. Microscopically, these tumors contain a variety of mature and immature tissue components. The immature elements almost always consist of immature neural tissue in the form of small round blue cells focally organized into rosettes and tubules (Fig. 11.2). There is a correlation between the disease prognosis and the degree of immaturity in the teratoma. The three-tiered grading system is still the one most often used. Grade 1 neoplasms display some immaturity, but the immature neural tissue does not exceed in aggregate the area of one low-power field (40 $\times$) in any slide. Grade 2 teratomas contain more immaturity, but immature neural tissue occupies no more than an area equal to three low-power fields in any slide. Grade 3 neoplasms contain immature neural tissue that occupies an area greater than three low-power fields in at least one slide. The amount of mitotic activity and immature neural tissue with rosettes and tubules also

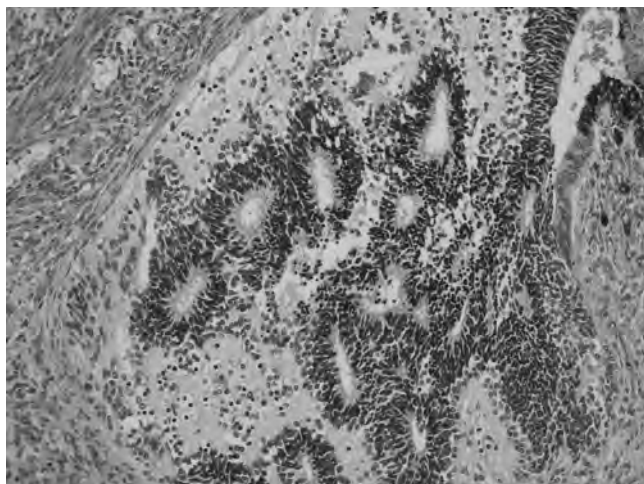


FIGURE 11.2. Ovarian IT. Immature neural tissue forms tubules.

increases with increasing tumor grade. Some authors prefer classifying ITs as either low- (grade 1) or high- (grades 2 and 3) grade teratomas. In patients whose neoplasm has disseminated beyond the ovary, the grade of the tumor metastasis is important in predicting survival and determining treatment. Occasionally, patients may have peritoneal implants that contain only mature tissue, but these mature glial implants may represent host tissue and not actual tumor implants. It is extremely important to sample peritoneal disease thoroughly in order that foci of IT (that may coexist with mature glia) are identified.

CLINICAL FEATURES

KEY POINTS

- Germ cell tumors account for 2% to 3% of all ovarian cancers and usually occur in girls or young women.
- Most present with stage I disease.
- hCG and AFP are useful tumor markers for some subsets of germ cell tumors.

Abdominal pain associated with a palpable pelvic-abdominal mass is present in approximately 85% of patients. Approximately 10% of patients present with acute abdominal pain, usually caused by rupture, hemorrhage, or ovarian torsion. This finding is somewhat more common in patients

with endodermal sinus tumor or mixed germ cell tumors and is frequently misdiagnosed as acute appendicitis. Less common signs and symptoms include abdominal distention (35%), fever (10%), and vaginal bleeding (10%). A few patients exhibit isosexual precocity, presumably due to hCG production by tumor cells.

Many germ cell tumors possess the unique property of producing biologic markers that are detectable in serum. The development of specific and sensitive radioimmunoassay techniques to measure hCG and AFP led to dramatic improvement in patient monitoring. Serial measurements of serum markers aid the diagnosis and, more importantly, are useful for monitoring response to treatment and detection of subclinical recurrences. Table 11.1 illustrates typical findings in the sera of patients with various tumor histologic types. Endodermal sinus tumor and choriocarcinoma are prototypes for AFP and hCG production, respectively. Embryonal carcinoma can secrete both hCG and AFP, but most commonly produces hCG. Mixed tumors may produce either, both, or none of the markers, depending on the type and quantity of elements present. Dysgerminoma is commonly devoid of hormonal production, although a small percentage of tumors produce low levels of hCG. The presence of an elevated level of AFP or high level of hCG (>100 U/mL) denotes the presence of tumor elements other than dysgerminoma. Therapy should be adjusted accordingly (see below). Although ITs are associated with negative markers, a few tumors can produce AFP. A third tumor marker is lactic dehydrogenase, which is frequently elevated in patients with dysgerminoma or other germ cell tumors. Unfortunately, it is less specific than hCG or AFP, which limits its usefulness. CA-125 can also be nonspecifically elevated in patients with ovarian germ cell tumors.

TABLE 11.1
SERUM TUMOR MARKERS IN MALIGNANT GERM CELL TUMORS OF THE OVARY

Histology	AFP	hCG
Dysgerminoma	–	±
Endodermal sinus tumor	+	–
IT	±	–
Mixed germ cell tumor	±	±
Choriocarcinoma	–	+
Embryonal carcinoma	±	+
Polyembryoma	±	+

SURGERY

KEY POINTS

- A substantial majority of patients with ovarian germ cell tumors are long-term survivors and suffer minimal morbidity from treatment.
- Fertility-sparing surgery procedures enable a large proportion of young women with ovarian germ cell tumors to preserve their reproductive potential.
- Secondary cytoreduction may be important for women whose tumors contain immature teratoma.

Operative Findings

Malignant germ cell tumors of the ovary tend to be quite large. Bilaterality of tumor involvement is exceedingly rare except for dysgerminoma. Ascites may be noted in approximately 20% of cases. Rupture of tumors, either preoperatively or intraoperatively, can occur in approximately 20% of cases.

Benign cystic teratoma is associated with malignant germ cell tumors in 5% to 10% of cases. These coexistent teratomas may occur in the ipsilateral ovary, in the contralateral ovary, or bilaterally. Likewise, a preexisting gonadoblastoma may be noted in association with dysgerminoma and dysgenetic gonads related to a 46,XY karyotype.

Malignant germ cell tumors generally spread in one of two ways: along the peritoneal surface or through lymphatic dissemination. They more commonly metastasize to lymph nodes than epithelial tumors. The stage distribution is also very different from that of epithelial tumors. In most large series, approximately 60% to 70% of tumors will be stage I, with stage III accounting for 25% to 30% of tumors. Stages II and IV are relatively uncommon.

Extent of Primary Surgery

The initial treatment approach for a patient suspected of having a malignant ovarian germ cell tumor is surgery, both for diagnosis and for therapy. After an adequate vertical midline incision, a thorough determination of disease extent by inspection and palpation should be made. If the disease is confined to one or both ovaries, it is imperative that proper staging biopsies be performed (see below).

The type of primary operative procedure depends upon the surgical findings. Because many of these patients are young women, for whom the preservation of fertility is a priority, minimizing the surgical resection while ensuring the removal of tumor bulk must be thoughtfully balanced. As noted previously, bilateral ovarian involvement is rare, except for the case

of pure dysgerminoma. Bilateral involvement may be found in cases of advanced disease (stages II to IV), in which there is metastasis from one ovary to the opposite gonad, or in cases of mixed germ cell tumors with dysgerminoma component. Therefore, fertility-sparing unilateral salpingo-oophorectomy with preservation of the contralateral ovary and of the uterus can be performed in most patients. If the contralateral ovary appears grossly normal on careful inspection, it should be left undisturbed. However, in the case of pure dysgerminoma, biopsy may be considered, because occult or microscopic tumor involvement occurs in a small percentage of patients. Unnecessary biopsy, however, may result in future infertility due to peritoneal adhesions or ovarian failure. If the contralateral ovary appears abnormally enlarged, a biopsy or ovarian cystectomy should be performed. If frozen examination reveals a dysgenetic gonad, or if there are clinical indications suggesting a hermaphrodite phenotype, then bilateral salpingo-oophorectomy is indicated. However, it is difficult to establish this diagnosis on frozen section. This determination should preferably be made by determining a normal female karyotype preoperatively. If benign cystic teratoma is found in the contralateral ovary, an event that can occur in 5% to 10% of patients, then ovarian cystectomy with the preservation of remaining normal ovarian tissue is recommended.

The advent of *in vitro* fertilization technology has had an impact on operative management. Convention has dictated that if a bilateral salpingo-oophorectomy is necessary, a hysterectomy should also be performed. However, with current assisted reproduction technologies (ART) involving donor oocyte and hormonal support, a woman without ovaries could potentially sustain a normal intrauterine pregnancy. Similarly, if the uterus and one ovary are resected because of tumor involvement, current techniques provide the opportunity for oocyte retrieval from the remaining ovary, *in vitro* fertilization with sperm from her male partner, and embryo implantation into a surrogate's uterus. As the field of ART is evolving, traditional guidelines concerning surgical treatment in young patients with gynecologic tumors have to be thoughtfully adapted to individual circumstances.

Surgical Staging

Surgical staging information is essential for determining the extent of disease, providing prognostic information, and guiding postoperative management. It is of critical importance for those patients with early clinical disease in order to detect the presence of occult or microscopic metastases. Staging of ovarian germ cell tumors follows the same principles applicable to epithelial ovarian tumors, as described by the International Federation of Gynecologists and Obstetricians (FIGO, see Table 11.2). Proper staging procedures consist of the following:

1. Although a transverse incision is cosmetically superior, a vertical midline incision is usually necessary for adequate exposure, appropriate staging biopsies, and resection of large pelvic tumors or metastatic disease in the upper abdomen.

TABLE 11.2**FIGO STAGING OF OVARIAN GERM CELL TUMORS**

Stage	Description
I	Tumor limited to ovaries
IA	Tumor limited to one ovary, no ascites, intact capsule
IB	Tumor limited to both ovaries, no ascites, intact capsule
IC	Tumor either stage IA or IB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings
II	Tumor involving one or both ovaries with extension to the pelvis
IIA	Extension to uterus or tubes
IIB	Involvement of both ovaries with pelvic extension
IIC	Tumor either stage IIA or IIB, but with ascites present containing malignant cells or with ovarian capsule involvement or rupture or with positive peritoneal washings
III	Tumor involving one or both ovaries with tumor implants outside the pelvis or with positive retroperitoneal or inguinal lymph nodes. Superficial liver metastases qualify as stage III
IIIA	Tumor limited to the pelvis with negative nodes but with microscopic seeding of the abdominal peritoneal surface
IIIB	Negative nodes, tumor implants in the abdominal cavity <2 cm
IIIC	Positive nodes or tumor implants in the abdominal cavity >2 cm
IV	Distant metastases present

2. Ascites, if present, should be evacuated and submitted for cytologic analysis. If no peritoneal fluid is noted, cytologic washings of the pelvis and bilateral paracolic gutters should be performed prior to manipulation of the intraperitoneal contents.
3. The entire peritoneal cavity and its structures should be carefully inspected and palpated in a methodical manner. The subdiaphragmatic areas, omentum, colon, all peritoneal surfaces, the entire retroperitoneum, and small intestinal serosa and mesentery should be checked. If any suspicious areas are noted, they should be submitted for biopsy or excised.
4. Next, the primary ovarian tumor and pelvis should be examined. Both ovaries should carefully be assessed for size, presence of obvious tumor involvement, capsular rupture, external excrescences or adherence to surrounding structures.

5. If disease seems to be limited, that is, confined to the ovary or localized to the pelvis, then random staging biopsies of structures at risk should be performed. These sites should include the omentum (with generous biopsies from multiple areas) and the peritoneal surfaces of the following sites: bilateral paracolic gutters, cul-de-sac, lateral pelvic walls, vesicouterine reflection, and subdiaphragmatic areas. Any adhesions should also be generously sampled.
6. The paraaortic and bilateral pelvic lymph node-bearing areas should be carefully palpated. Any suspicious nodes should be excised or sampled. If no suspicious areas are detected, these areas should be sampled. There is no evidence that a complete paraaortic or pelvic lymphadenectomy is advantageous.
7. If obvious gross metastatic disease is present, it should be excised if feasible, or at least sampled to document disease extent. The concept of cytoreductive surgery is discussed below.

Most patients still undergo initial surgery in community hospitals and are inadequately staged. Upon referral of such a patient to a university or tertiary care center, the oncologist is faced with the dilemma of inadequate staging information. In such cases, postoperative studies including computed tomography of the abdomen are recommended. If histopathologic and limited anatomic information from the first surgery clearly indicates the use of systemic chemotherapy, it is generally inadvisable to consider reexploration solely for the purpose of precise staging information. Re-operation to complete comprehensive staging may be appropriate under clinical circumstances where careful surveillance observation after complete staging may be a sensible alternative to chemotherapy.

Cytoreductive Surgery

If widely spread tumor is encountered at initial surgery, it is recommended that the same principles concerning primary cytoreductive surgery applied in the surgical management of advanced epithelial ovarian cancer be followed. As much tumor should be resected as is technically feasible and safe. It is clear that patients with completely resected disease do better than those with bulky postoperative residual disease. However, as with epithelial tumors, the relative influence of tumor biology, surgical skill, and aggressiveness remain uncertain. Germ cell tumors, especially dysgerminomas, are generally much more chemosensitive than epithelial ovarian tumors. Therefore, aggressive resection of metastatic disease in these cases, especially resection of bulky retroperitoneal nodes, is questionable. Even in the face of extensive metastatic disease, it is generally possible to perform a fertility-sparing procedure with preservation of a normal contralateral ovary.

The value of secondary cytoreductive surgery in the management of malignant ovarian germ cell tumors is even less clear than that of primary cytoreductive surgery. The finding of a residual mass after completion of chemotherapy is less common in patients with ovarian germ cell tumors than in men with testis cancer, because the women are likely to have considerable tumor debulking at the time of the diagnostic surgical procedure

and thus enter chemotherapy with significantly less tumor burden. At the completion of chemotherapy, men with nonseminomatous tumors or seminoma may have persistent mature teratoma or desmoplastic fibrosis. In patients with bulky dysgerminoma, residual masses after chemotherapy are very likely to represent desmoplastic fibrosis. Although a number of patients with pure ovarian ITs or mixed germ cell tumors have persistent mature teratoma at the completion of chemotherapy, the majority are left with multiple small peritoneal implants rather than with a dominant mass. However, occasional patients who have received chemotherapy for IT or mixed germ cell tumor containing teratoma will have bulky residual teratoma after chemotherapy. In testis cancer, patients with bulky residual teratoma may experience slow progression of tumor or may develop overtly malignant tumors over time. There are similar anecdotal reports of progressive mature teratoma in ovarian germ cell tumor patients after chemotherapy. Mature teratoma is not chemotherapy sensitive. Considering this information, it seems appropriate to resect persistent masses in patients with negative markers after chemotherapy for germ cell tumors containing IT. If viable malignant neoplasm is found, additional chemotherapy should be considered. However, if only mature teratoma is resected, observation is generally recommended.

Second-Look Laparotomy

Second-look laparotomy was formerly included in the routine management of patients with epithelial ovarian cancer to assess disease status after a fixed interval of chemotherapy. The term generally applies to surgery performed in patients with no clinical evidence of disease (in contrast to the term “secondary cytoreductive surgery,” where there is generally evidence of disease to be removed). Currently, second-look surgery is not considered to be of benefit in women with germ cell tumors who had complete tumor resection with primary surgery. There is also not any apparent benefit of second-look surgery in most patients with incomplete tumor resection at initial surgery. The exception is the subgroup of patients with incompletely resected tumors containing teratoma elements. They may have residual bulky or progressive mature teratoma or residual IT at second-look surgery, and clinical benefit can be derived by further resection.

Advances in imaging technology, including the advent of positron emission tomography (PET) scanning, may further decrease the need for surgical reexploration. However, while PET scan is sensitive for detecting active (malignant) tumor, its usefulness in evaluating residual mature teratoma is more limited. A positive PET scan in the setting of a residual mass after treatment is highly indicative of viable tumor and when used in conjunction with traditional radiographic techniques (CT scan and MRI) and tumor marker determinations can predict relapses with accuracy. A recent series demonstrates that in patients with residual masses after treatment for seminoma, a positive PET scan is strong evidence that the residual mass contains persistent tumor. In contrast, if the PET scan is negative, the residual mass is very unlikely to contain tumor.

CHEMOTHERAPY FOR OVARIAN GERM CELL TUMORS

KEY POINTS

- The risk of relapse with surgery alone is unacceptably high for most women with germ cell tumors.
- Stage IA grade 1 immature teratomas may be observed as they rarely relapse.
- Stage I dysgerminomas may be observed, as they can generally be cured with surgery at the time of relapse.
- For most other women, three to four cycles of bleomycin, etoposide, and cisplatin are recommended.
- Dysgerminomas are particularly chemotherapy sensitive.
- High-dose chemotherapy with stem cell rescue may cure some women who relapse after initial chemotherapy.

Chemotherapy

One of the great triumphs of cancer treatment in the 1970s and 1980s was the development of effective chemotherapy for testicular germ cell tumors. The lessons learned from prospective, randomized trials in testis cancer have been applied to ovarian germ cell tumors. Presently, the overwhelming majority of patients with ovarian germ cell tumors survive their disease with the judicious use of surgery and cisplatin-based combination chemotherapy.

Historically, the first regimens used successfully for women with ovarian germ cell tumors were VAC (vincristine, dactinomycin, and cyclophosphamide) or VAC-type regimens. However, among patients with advanced disease, the number of long-term survivors after VAC therapy remained under 50%. Based on promising results obtained in men with testicular cancer, a prospective Gynecologic Oncology Group (GOG) study that evaluated BEP (bleomycin, etoposide, and cisplatin) was performed in patients with ovarian germ cell tumors. The regimen was highly effective, with 91 of 93 enrolled patients free of disease at follow-up. Based on these data, although BEP and VAC have not been prospectively compared, BEP emerged as the preferred regimen for patients with ovarian germ cell tumors.

Differences in Outcome for Patients with Completely Resected Tumors Versus Advanced Stage Disease

In the hands of an experienced surgeon, the majority of women with ovarian tumors are debulked to minimal and often clinically undetectable disease before starting chemotherapy. Therefore, unlike patients with testis cancer, most women who are candidates for chemotherapy have minimal

or no residual disease. However, the anticipated risk of relapse with surgery alone in patients with advanced disease is as high as 75% to 80%. Patients with embryonal carcinoma, endodermal sinus tumors, and mixed tumors containing these elements are considered to be at particularly high risk of recurrence without postoperative therapy. This risk can be minimized by the use of adjuvant chemotherapy. In GOG-78, 50 of 51 patients with completely resected ovarian germ cell tumors remained with no evidence of disease (NED) when three cycles of BEP were given adjuvantly. Other studies using cisplatin-based therapy have given similar results. The recommended treatment for most patients with completely resected tumors (with the exception of patients with grade 1, stage IA IT or stage IA dysgerminoma) is adjuvant chemotherapy with three courses of BEP.

In contrast, most clinical series have shown worse clinical outcome for patients with metastatic disease or with incompletely resected tumors with progression-free survival rates after surgery and chemotherapy ranging from 53% to 91%. Clinical prognosticators for outcome of malignant ovarian germ cell tumors are stage at diagnosis and increase in tumor markers. However, a dependable risk stratification, as the one used for testis tumors, is not currently in use.

Management of Residual or Recurrent Disease

The large majority of patients with ovarian germ cell tumors are cured with surgery and platinum-based chemotherapy. However, a small percentage of patients have persistent or progressive disease during treatment or recur after the completion of treatment. Most recurrences occur within 24 months from primary treatment. Like in testis cancer, these treatment failures are categorized as platinum resistant (progression during or within 4 to 6 weeks of completing treatment) or platinum sensitive (recurrence beyond 6 weeks from platinum based therapy).

The management of recurrent disease is complex and is preferably performed in a specialized center. Data to guide the management of patients with recurrent ovarian germ cell tumors are scant and largely extrapolated from the clinical experience with testicular cancer. The single most important prognostic factor in patients with testis cancer is whether or not they are refractory to cisplatin. The likelihood of cure with high-dose salvage therapy in patients who relapse from a complete remission after initial therapy is as high as 60% or more. On the other hand, in patients who are truly cisplatin refractory, only 30% to 40% will be long survivors. Approximately 30% of patients with recurrent platinum-sensitive testis cancer can be salvaged with second-line chemotherapy (VeIP: vinblastine, ifosfamide, platinum). However, there is now strong evidence that high-dose therapy with carboplatin, etoposide with or without cyclophosphamide or ifosfamide and stem cell rescue is superior to standard dose salvage therapy for these patients. While this approach has not been prospectively tested in women with recurrent platinum-sensitive ovarian germ cell tumors, because of the small numbers of patients, the concepts are very similar and support the use of high-dose therapy in this setting.

Referral to a specialized center for management of recurrent disease is desirable.

Active agents in the setting of recurrence after high-dose chemotherapy include ifosfamide, taxanes, and gemcitabine. In one phase II trial from Indiana University, the combination of gemcitabine and paclitaxel induced objective responses in 10 of 31 patients who had recurred after high-dose chemotherapy. Of those, five patients were free of disease at 2 years after treatment.

Immediate Toxicity of BEP Chemotherapy

KEY POINTS

Acute toxicities of BEP chemotherapy include the following:

- Neutropenic fever
- Nausea/vomiting
- Pulmonary fibrosis (bleomycin)
- Renal toxicity (cisplatin)
- Ototoxicity (cisplatin)
- Peripheral neuropathy (cisplatin)

Acute adverse effects of chemotherapy can be substantial and these patients should be treated by physicians experienced in their management. About 25% of patients develop febrile neutropenic episodes during chemotherapy and require hospitalization and broad-spectrum antibiotics. Cisplatin is associated with nephrotoxicity, which can be minimized by ensuring adequate hydration during and immediately after chemotherapy and by avoidance of aminoglycoside antibiotics. Bleomycin can cause pulmonary fibrosis. Pulmonary function testing has been used to follow these patients. However, the value of carbon monoxide diffusion capacity to predict early lung disease has been challenged. The most effective method for monitoring germ cell tumor patients is careful physical examination of the chest. Findings of early bleomycin lung disease are a lag or diminished expansion of one hemi-thorax or fine basilar rales that do not clear with cough. These findings can be very subtle but if present mandate immediate discontinuation of bleomycin. It is important to note that randomized trials in good prognosis testis cancer have suggested that bleomycin is an important component of the treatment regimen, particularly if only three courses of therapy are given. Other randomized trials have shown that carboplatin is inferior to cisplatin and cannot be substituted for cisplatin without worsening therapeutic outcome.

Patients with advanced ovarian germ cell tumors should receive three to four courses of treatment given in full dose and on schedule. As most patients are young and will not develop neutropenic fever or infection, hematopoietic growth factors are not routinely necessary, but it is reasonable to use them to avoid dose reductions for patients with previous episodes of neutropenic fever or in unusually ill patients who are at a higher risk of myelosuppressive complications, or those who received prior radiotherapy. Modern antiemetic therapy has greatly lessened chemotherapy-induced emesis. Chemotherapy-related mortality should be less than 1%.

IMMATURE TERATOMA

The management of patients with IT is complex. As discussed above (see pathology), ITs are categorized as grades 1, 2, or 3 depending on the amount of immature neuroepithelium in the tumor. Our current appreciation of recurrence risk in these patients is based on an early study by Norris. Only 1 of 14 patients with grade 1 IT recurred, while 13 of 26 patients with grade 2 and 3 tumors recurred. This study set the current standard of care for women with stage I teratoma, which is surveillance for grade 1 IT and adjuvant chemotherapy with three courses of BEP for patients with grade 2 and 3 tumors. However, a significant limitation of the Norris report is the probable underestimation of tumor stage. In the modern era of complete surgical staging of ovarian neoplasms, it might be appropriate to reconsider the role of routine adjuvant therapy in these patients. Several groups have reported their experience with surveillance.

First, an Intergroup study of the Pediatric Oncology Group and the Children's Cancer Group reported that surveillance after complete surgical resection in 41 girls with ovarian IT was sufficient. Only one recurrence, which was salvaged with BEP, was noted during 24 months of follow-up. Of note is that in this series, 13 patients had grade 2 and 3 IT and 10 patients had mixed tumors containing IT plus yolk sac tumor.

Second, investigators at Mount Vernon and Charing Cross Hospitals in England observed 15 patients with stage IA tumors after initial surgical resection. Of these, nine patients had grade 2 or 3 IT and six had elements of endodermal sinus tumor. There were three recurrences in this series, 1/9 in the pure IT group and 2/6 in the mixed histology group. Two of these patients were salvaged with chemotherapy and one patient died of pulmonary embolus. Of note is that the patient who died became pregnant 4 months after diagnosis and could not be followed adequately due to her pregnancy.

Third, investigators at the University of Milan reported the clinical outcome in a group of 32 patients with pure ovarian IT followed prospectively. In this group, nine patients had grade 2 and 3 stage IA ITs and were treated with surgery and intensive surveillance. Only two recurrences were noted in this group. They consisted of one case of mature teratoma and one case of gliosis. The mature teratoma was resected and the patient with gliosis was followed without treatment. Both patients are alive and well and never received chemotherapy. Among four patients with stage IC tumors treated with surgical resection and surveillance, there was one case of gliosis and one recurrence with mature tissue, which was resected (no chemotherapy). All patients are currently free of disease.

When considering these issues, it is important to not overstate the toxicities of adjuvant therapy. While it may be appropriate to consider surveillance with careful follow-up in well-staged adult patients with ovarian stage IA IT, this plan of care has not been tested prospectively and should be approached with caution.

DYSGERMINOMA

Dysgerminoma is the female equivalent of seminoma. This disease differs from its nondysgerminomatous counterparts in several respects. First, it is more likely to be localized to the ovary at the time of diagnosis (stage I). Bilateral involvement is more common, as is spread to retroperitoneal lymph nodes. While it is less relevant now than before the era of modern chemotherapy, dysgerminoma is very sensitive to radiation.

Observation for Stage I Tumors

As many as 75% to 80% of dysgerminoma patients used to be considered stage I at diagnosis. With more precise surgical staging, the true figure is probably somewhat lower. Currently, patients with well-staged IA dysgerminoma can be observed after unilateral salpingo-oophorectomy, regardless of the size of the primary tumor. Careful follow-up is required, because as many as 15% to 25% of patients will experience a recurrence. However, because of the tumor's chemosensitivity, virtually all dysgerminoma patients can be salvaged successfully at the time of recurrence, if detected early.

Chemotherapy

Dysgerminoma is very responsive to cisplatin-based chemotherapy, even more so than other germ cell tumors. Therefore, less toxic chemotherapy has been considered. An alternative regimen tested by the GOG consists of a 3-day regimen with carboplatin and etoposide. On this protocol, all 39 patients with pure dysgerminoma remained free of disease at a median follow-up of 7.8 years. Although highly active, this regimen is not recommended for routine use, because significantly less experience has accumulated with its use and there is concern that this regimen is not as effective in tumors containing nondysgerminomatous elements.

The implications of elevated hCG or AFP levels in patients with dysgerminoma should be emphasized. These tumor markers are usually increased in patients with nondysgerminomatous tumors. Therefore, AFP elevation denotes the presence of elements other than dysgerminoma and treatment should be tailored accordingly. An elevated hCG level can be occasionally seen in pure dysgerminoma. This finding should not alter therapy, but prompt reexamination of the tumor specimen to determine whether syncytiotrophoblastic cells are present or, if the tumor contains nondysgerminomatous elements.

LATE EFFECTS OF TREATMENT

KEY POINTS

Late toxicities of BEP chemotherapy

- Secondary leukemia and other malignancies (etoposide)
- Most young women maintain fertility after BEP

Sequelae of Surgery

Although there is no available information on the long-term effects of surgery on patients with germ cell tumors, future infertility related to pelvic surgery with subsequent peritoneal and tubal adhesions is well described. Therefore, meticulous surgical technique and avoidance of unnecessary operative maneuvers (e.g., biopsy of a normal contralateral ovary) are required for preventing future complications.

Recently, Gershenson reported that among 132 survivors of ovarian germ cell tumors treated with surgery and platinum based chemotherapy, 71 patients had fertility-sparing procedures. Of those potentially fertile survivors, 62 (87.3%) maintained menstrual periods and 24 survivors reported 37 successful pregnancies. Although the survivors reported an increased incidence of gynecologic problems and diminished sexual pleasure, they also tended to have stronger, more positive relationships with their significant others.

As with any group of patients with the history of pelvic surgery, patients with malignant ovarian germ cell tumors may develop functional cysts in the residual ovary. A trial of oral contraceptives and serial ovarian surveillance with sonography is helpful in distinguishing functional cysts from tumor recurrence.

Sequelae of Chemotherapy

As noted above, most women treated with BEP chemotherapy maintain fertility, and there is no current evidence for an increased incidence of birth defects in subsequent offspring.

A recently recognized effect of chemotherapy used for the treatment of germ cell tumors is the risk of secondary malignancies. The epipodophylotoxins, including etoposide, are associated with the development of acute myelogenous leukemia (AML). Morphologically, these leukemias are monocytic or myelomonocytic (M4 or M5). Characteristic chromosomal translocations (mostly involving the 11q23 region) are frequently, but not always, present. Leukemia after etoposide treatment occurs within 2 to 3 years, which is different from alkylating agent-induced AML, which has a longer latency period. This treatment complication appears to be dose- and schedule-dependent. Of 348 male germ cell tumor patients receiving three to four courses of BEP as first line therapy at Indiana University, two developed etoposide-related leukemia. None of 67 patients who received only three courses developed AML. In the GOG protocol testing the efficacy of BEP in women with ovarian germ cell tumors, one case of AML was recorded among 91 patients treated.

In male patients who received cisplatin-based combination regimens, principally cisplatin/vinblastine/bleomycin (PVB), late toxicities described include high tone hearing loss, neurotoxicity, Raynaud phenomenon, ischemic heart disease, renal dysfunction, and pulmonary toxicity. Fortunately, despite these observations, most patients have excellent overall health and functional status. The GOG recently completed an analysis evaluating the quality of life and psychosocial characteristics of survivors of ovarian germ

cell tumors compared to matched controls. In this analysis, the survivors appeared to be well adjusted, were able to develop strong relationships, and were free of significant depression. The impact on fertility was modest or none in patients undergoing fertility sparing surgeries. Overall, these women appeared to be free of any major physical illnesses at a median follow-up of 10 years.

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CHAPTER 12 ■ MOLAR PREGNANCY AND GESTATIONAL TROPHOBLASTIC NEOPLASMS

EPIDEMIOLOGY

KEY POINTS

- The frequency of molar pregnancy in Asia is seven to ten times greater than in the United States or Europe.
- One in three pregnancies in women over the age of 50 is molar.
- Gestational trophoblastic neoplasms most commonly follow a molar pregnancy but may develop after any gestation.

Molar pregnancy and gestational trophoblastic neoplasms (GTN) comprise a group of interrelated diseases including complete and partial molar pregnancies, invasive mole, placental site trophoblastic tumor (PSTT), and choriocarcinoma (CCA) that have varying propensities for local invasion and metastasis. GTN are among the rare human malignancies that are highly curable with chemotherapy even with widespread metastases. Although GTN most commonly follow a molar pregnancy, they may develop after any gestation.

The reported incidence of GTN varies dramatically in different regions of the world. The frequency of molar pregnancy in Asian countries is seven to ten times greater than the reported incidence in North America or Europe. Whereas hydatidiform mole occurs in Taiwan in 1 per 125 pregnancies, the incidence of molar gestation in the United States is about 1 per 1,500 live births.

The risk of having a complete hydatidiform mole (CHM), although not the risk for a partial hydatidiform mole (PHM), also increases with advanced maternal age. Women over 40 years of age have a 5- to 10-fold greater risk of CHM. In fact, one out of three pregnancies in women over 50 years of age is molar and the risk of developing GTN is significantly increased as well.

The risk for both complete and partial molar pregnancies is also increased in women with a history of prior spontaneous abortion and infertility.

MOLAR PREGNANCY

KEY POINTS

- Hydatidiform moles may be categorized as either complete or partial based upon gross morphology, histopathology, and karyotype.
- Most complete moles have a 46,XX karyotype with entirely paternal chromosomes.
- Most partial moles have a triploid karyotype.
- Complete moles often present with bleeding and a markedly elevated human chorionic gonadotropin (hCG).
- Partial moles generally present as a missed abortion.

CHMs have no identifiable embryonic or fetal tissues. The chorionic villi have generalized swelling and diffuse trophoblastic hyperplasia, and the implantation site trophoblast has diffuse, marked atypia. Complete moles usually have a 46,XX karyotype, and the molar chromosomes are derived entirely from paternal origin. Most of the complete moles appear to arise from an anuclear empty ovum that has been fertilized by a haploid (23X) sperm, which then duplicates its own chromosomes. Approximately 10% of complete moles have a 46,XY karyotype. The 46,XY complete mole arises from fertilization of an anuclear empty ovum by two sperm. Whereas chromosomes in the complete mole are entirely of paternal origin, the mitochondrial DNA is of maternal origin.

Familial recurrent hydatidiform mole (FRHM) is a rare syndrome characterized by recurrent CHMs of biparental, rather than the more usual androgenetic, origin. A specific gene defect in these families has not been identified, but genetic mapping has shown that in most families the gene responsible is located in a 1.1 Mb region on chromosome 19q13.4. Subsequent pregnancies in women diagnosed with this condition are likely to be CHM. Molar pregnancies in women with FRHM are associated with consanguinity and have a risk of progressing to GTN similar to that of androgenetic CHM.

PHMs are characterized by the following pathologic features: (a) varying-sized chorionic villi with focal swelling and focal trophoblastic hyperplasia, (b) focal, mild atypia of implantation site trophoblast, (c) marked villous scalloping and prominent stromal trophoblastic inclusions, and (d) identifiable fetal or embryonic tissues (Fig. 12.1). Partial moles generally have a triploid karyotype, which results from the fertilization of an apparently normal ovum by two sperm. When fetuses are identified with partial moles, they generally have stigmata of triploidy including growth retardation and multiple congenital anomalies.

Studies have recently shown that immunohistochemistry for p57 is useful for confirming the diagnosis of CHM. Almost all complete moles have absent (or near absent) villous stromal and cytotrophoblastic nuclear activity for p57, while all other types of gestations (including partial moles) show nuclear reactivity in more than 25% of villous stromal and cytotrophoblastic nuclei.

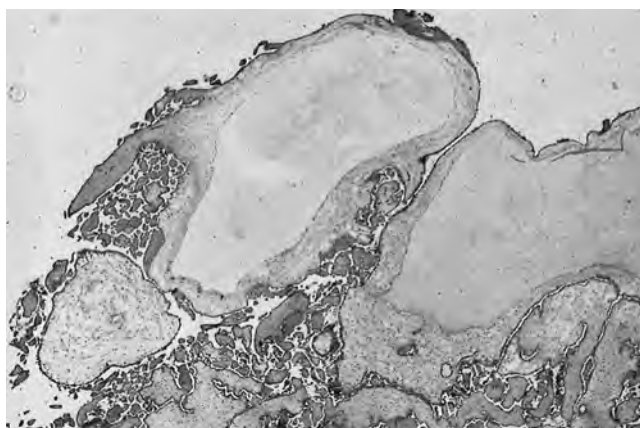


FIGURE 12.1. Photomicrograph of a PHM demonstrating varying-sized chorionic villi with focal swelling and focal trophoblastic hyperplasia.

Complete Hydatidiform Mole

Vaginal bleeding is the most common presenting symptom in patients with CHM. The measurement of markedly elevated hCG values is suggestive of the diagnosis. Theca lutein cysts, resulting from hyperstimulation of the ovaries by high circulating levels of hCG, are found in up to half of patients. Symptoms associated with very high hCG levels, such as excessive uterine enlargement at gestational age, hyperemesis gravidarum, and preeclampsia, are less common now than in previous years, as CHM is being diagnosed at an earlier stage. Hyperthyroidism, resulting in thyroid storm at the time of anesthesia induction, and respiratory insufficiency resulting from multiple causes, including preeclampsia and embolization of molar tissue to the pulmonary vasculature, are also much less common than before. Ultrasonography is a sensitive and reliable technique for diagnosis. Because of marked swelling of the chorionic villi, a complete mole produces a characteristic vesicular sonographic pattern.

CHMs are well recognized to have the potential for developing uterine invasion or distant spread. Following molar evacuation, uterine invasion and metastasis occur in 15% and 4% of the patients, respectively. Most centers in the United States define postmolar persistent GTN by the presence of a re-elevation or persistent plateau in hCG for at least 3 consecutive weeks. The trend to earlier diagnosis of CHM does not appear to have affected the incidence of postmolar tumors.

Factors that predispose to postmolar tumors include signs of marked trophoblastic proliferation including hCG level of more than 100,000 mIU/mL, uterine size greater than that at gestational age, and theca lutein cysts more than 6 cm in diameter. An increased risk of postmolar GTN has also been observed in women over 40 years of age and women with multiple molar pregnancies.

Partial Hydatidiform Mole

The patients generally present with the signs and symptoms of missed or incomplete abortion. The diagnosis of partial mole is usually made after histologic review of curettage specimens. Sonographic findings significantly associated with the diagnosis of partial mole include focal cystic changes in the placenta and a ratio of the transverse to anteroposterior dimension of the gestational sac greater than 1.5. Patients with PHM do not present with markedly elevated hCG values as often as the patients with CHM. Complete and partial moles also differ in their levels of free β - and α -subunits of hCG. Whereas complete moles have higher levels of percentage free β -hCG, partial moles have higher levels of percentage free α -hCG. The mean ratios of percentage free β -hCG to free α -hCG in complete and partial moles are 20.9 and 2.4, respectively. The risk of developing GTN following PHM has been reported from 0% to 11%.

Surgical Evacuation

KEY POINTS

- Surgical evacuation is the treatment of choice for molar pregnancy.
- The use of prophylactic chemotherapy at the time of surgery remains controversial.
- After molar evacuation women should be followed with hCG levels until the levels have been normal for 6 months.
- Women should avoid pregnancy during the period of hormonal follow-up.

After diagnosis of a molar pregnancy, the patient should be carefully evaluated to identify the potential presence of medical complications including preeclampsia, electrolyte imbalance, hyperthyroidism, and anemia that might complicate surgical evacuation. If the patient no longer desires to preserve fertility, hysterectomy may be performed. Prominent theca lutein ovarian cysts may be aspirated at the time of surgery. Although hysterectomy eliminates the risks of local invasion, it does not prevent metastasis.

Suction curettage is the preferred method of evacuation in patients who desire to preserve fertility. As the cervix is being dilated, the surgeon may encounter brisk uterine bleeding due to the passage of retained blood. Shortly after commencing suction evacuation, uterine bleeding is generally well controlled and the uterus rapidly regresses in size. If the uterus is larger than 14-weeks size, one hand should be placed on top of the fundus and the uterus should be massaged to stimulate uterine contraction. When suction evacuation is thought to be complete, a sharp curettage should be performed to remove any residual chorionic tissue. Patients who are Rh negative should receive Rh immune globulin at the time of evacuation because Rh D factor is expressed on trophoblast.

Role of Prophylactic Chemotherapy

The use of prophylactic chemotherapy at the time of molar evacuation remains controversial. In one trial, chemoprophylaxis significantly reduced the incidence of postmolar tumor from 47% to 14% in patients with high-risk complete moles, but did not significantly influence the occurrence of persistent tumors in patients with low-risk complete moles. Chemoprophylaxis may be useful if it is suspected that the patient will be lost to follow-up. Massad et al. observed that among 40 indigent women with molar pregnancy, 33 (82%) did not fully comply with hCG follow-up and 5 (13%) were lost to follow-up before remission.

Hormonal Follow-Up

After molar evacuation, patients should be followed with weekly hCG values until they are normal for 3 weeks, and then with monthly values until they are normal for 6 months. After achieving nondetectable hCG levels, the risk of relapse appears to be very low.

The patients should be encouraged to use effective contraception during the entire interval of follow-up. Intrauterine devices should not be inserted until the patient achieves normal hCG levels because of the risk of uterine perforation, bleeding, and infection if residual tumor is present. Options include surgical sterilization, hormonal contraceptives, or barrier methods.

GESTATIONAL TROPHOBLASTIC NEOPLASMS

KEY POINTS

- The diagnosis of gestational trophoblastic neoplasms should be considered in any woman in the reproductive age group with unexplained systemic or pulmonary symptoms.
- Metastases are very vascular and bleed easily. Biopsy should be approached with caution.
- Staging differs from that of most common solid tumors and involves a “risk score.”

Pathologic Considerations

After a molar pregnancy, persistent GTN may have the histologic pattern of either molar tissue or CCA. Gestational CCA does not contain chorionic villi, but is composed of sheets of both anaplastic cytotrophoblast and syncytiotrophoblast. PSTT is an uncommon variant of CCA. This tumor is composed almost entirely of mononuclear intermediate trophoblast and does not contain chorionic villi. Because PSTTs secrete very small amounts

of hCG, a large tumor burden may be present before hCG levels are detectable. PSTTs are associated with a higher percentage of free β -hCG which can contribute to diagnosis.

Natural History

Nonmetastatic Disease

Locally invasive GTN develop in 15% of patients following evacuation of a complete mole and infrequently after other gestations. An invasive trophoblastic tumor may perforate through the myometrium, producing intraperitoneal bleeding, or erode into uterine vessels, causing vaginal hemorrhage. A bulky necrotic tumor may also serve as a nidus for infection.

Metastatic Disease

Metastatic GTN occur in 4% of patients after evacuation of CHM and infrequently after other pregnancies. The most common metastatic sites are the lung (80%), vagina (30%), brain (10%), and liver (10%). Because trophoblastic tumors are perfused by fragile vessels, metastases are often hemorrhagic. The patients may present with signs and symptoms of bleeding from metastases such as hemoptysis, intraperitoneal bleeding, or acute neurologic deficits. Cerebral and hepatic metastases are uncommon unless there is concurrent involvement of the lungs and/or vagina.

Patients with pulmonary metastases commonly have asymptomatic lesions on chest radiography but may present with dyspnea, chest pain, cough, or hemoptysis. Trophoblastic emboli may cause pulmonary arterial occlusion and lead to right-heart strain and pulmonary hypertension. Gynecologic symptoms may be minimal or absent, and the antecedent pregnancy may be remote in time. The patient may be thought to have a primary pulmonary disease because respiratory symptoms may be dramatic.

Vaginal lesions may present with irregular bleeding or purulent discharge and are most commonly located in the fornices, or suburethrally. Vaginal metastases are highly vascular and may bleed vigorously if biopsied. Biopsy of vaginal metastases should be absolutely avoided; the desire to avoid hemorrhage should supersede the interest of obtaining an unequivocal pathologic diagnosis.

Staging System

The International Federation of Gynecology and Obstetrics (FIGO) reports data on GTN, using an anatomic staging system (Table 12.1). Patients with stage IV disease are most likely to be resistant to chemotherapy. Stage IV tumors generally have the histologic pattern of CCA and commonly follow a nonmolar pregnancy, with protracted delays in diagnosis and large tumor burdens.

The World Health Organization (WHO) has published a prognostic scoring system that reliably predicts the potential for chemotherapy resistance (Table 12.2). When the prognostic score is 7 or greater, the patient

TABLE 12.1

FIGO ANATOMIC STAGING FOR GESTATIONAL TROPHOBLASTIC NEOPLASIA

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, and broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

is considered to be at “high-risk” and requires intensive combination chemotherapy for optimal results. In general, patients with stage I disease have a low-risk score and patients with stage IV disease have a high-risk score. Therefore, the distinction between low-risk and high-risk primarily applies to stages II and III.

Diagnostic Evaluation

All patients should undergo a complete history and physical examination, a baseline hCG level, hepatic, thyroid, and renal function tests, and chest radiograph. Occult pulmonary metastases may be detected by computed tomographic (CT) scan in about 40% of patients with presumed nonmetastatic disease. If the chest X-ray is negative a CT scan should be obtained. Asymptomatic patients with a normal pelvic examination and negative chest CT are very unlikely to have liver or brain metastases identified by further radiographic studies. However, patients with vaginal or lung metastases and/or a pathologic diagnosis of CCA should undergo either a CT scan or magnetic resonance imaging scan of the head and abdomen to exclude brain and liver involvement. Pelvic ultrasonography may be useful to detect extensive uterine involvement by trophoblastic tumor and to identify sites of resistant uterine disease.

Management

KEY POINTS

- Most patients will be cured with chemotherapy.
- Low-risk patients (prognostic score ≤ 6) should be treated with single-agent chemotherapy.
- High-risk patients should receive combination chemotherapy.
- The use of etoposide appears to improve outcomes in high-risk patients, but carries a risk of secondary malignancies, including leukemia.

TABLE 12.2
MODIFIED WHO PROGNOSTIC SCORING SYSTEM AS ADAPTED BY FIGO

Scores	0	1	2	4
Age	<40	>40	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	<4	4–7	7–13	>13
Pretreatment serum hCG (IU/L)	<1,000	<10,000	<100,000	>100,000
Largest tumor size (including uterus)	—	3 to <5 cm	>5 cm	—
Site of metastases	Lung	Spleen/ kidney	GI	Liver/brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	Two or more drugs

Note: Format for reporting to FIGO Annual Report: In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in arabic numerals, e.g., stage II:4, stage IV:9. This stage and score will be allotted for each patient. FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization.

Stage I

Table 12.3 reviews the New England Trophoblastic Disease Center (NETDC) protocol for the management of stage I disease. The selection of treatment is based mainly on the patient's desire to preserve fertility. If the patient no longer wishes to retain fertility, hysterectomy with adjuvant single-agent chemotherapy may be performed as primary treatment. Chemotherapy may be safely administered at the time of hysterectomy without increasing operative complications.

Single-agent chemotherapy is the preferred treatment in patients with stage I disease who desire to retain fertility. Primary single-agent chemotherapy induced complete remission in 419 (84%) of 502 patients with stage I GTN. The remaining 83 resistant patients subsequently attained remission with either combination chemotherapy or surgical intervention. Whereas methotrexate (MTX) and actinomycin D (ACT D) are the two most commonly used single agents in the treatment of GTN in the United States and in most parts of the world, 5-fluorouracil has been the preferred single-agent chemotherapy in China.

Nonmetastatic PSTT should generally be treated with primary hysterectomy because this tumor responds less well to chemotherapy. A long

TABLE 12.3

TREATMENT PROTOCOLS FOR STAGE I GTN (NETDC)

INITIAL Sequential MTX/ACT D Hysterectomy (with adjunctive single-agent chemotherapy)
RESISTANT TO BOTH SINGLE AGENTS MAC EMACO, if MAC fails Hysterectomy (with adjunctive multiagent chemotherapy) Local uterine resection (for localized lesion, to preserve fertility)
FOLLOW-UP 12 consecutive months of nomal hCG levels Contraception mandatory

MTX, methotrexate; ACT D, actinomycin D; MAC, methotrexate, actinomycin D, cytoxan; EMACO, etoposide, methotrexate, actinomycin D, cytoxan, oncovin.

interval from the antecedent pregnancy to clinical presentation has been reported to be the most important prognostic factor for women with nonmetastatic PSTT. In one series, all 27 patients survived when the interval from the antecedent pregnancy was less than 4 years; all 7 patients died when the time interval exceeded 4 years.

Stages II and III

Low-risk patients (prognostic score <7) can be optimally treated with primary single-agent chemotherapy (Table 12.4). High-risk patients (prognostic score of 7 or above) should receive combination chemotherapy as the primary modality. Summarizing the experience from four centers, single-agent chemotherapy induced complete remission in 128 (87%) of 147 patients with low-risk metastatic GTN. All but two patients who were resistant to single-agent chemotherapy later achieved remission with combination chemotherapy.

Thoracotomy has a limited role in the management of stage III GTN. Thoracotomy should be performed if the diagnosis is seriously in doubt. Furthermore, if a patient has an isolated persistent viable pulmonary nodule despite intensive chemotherapy, pulmonary resection may be performed. It should be realized that fibrotic nodules may persist indefinitely on the chest radiograph after complete hCG remission is achieved. If a metastasis is persistent on radiography, but is of questionable viability, either a scan with a radioisotope-labeled antibody to hCG or a PET scan may be useful.

Hysterectomy may be required in patients with metastatic GTN to control uterine hemorrhage or sepsis. Furthermore, in patients with bulky uterine tumor, hysterectomy may reduce the tumor burden and thereby limit the need for chemotherapy. Angiographic embolization can also be effective in the management of profuse uterine bleeding in lieu of hysterectomy, especially in those patients who are hemodynamically stable and wish to retain their fertility potential.

TABLE 12.4
TREATMENT PROTOCOL FOR STAGES II AND III GTN (NETDC)

LOW RISK	
Initial therapy	Sequential MTX/ACT D
Resistant therapy	MAC or EMACO Surgery, as indicated
HIGH RISK	
Initial therapy	EMACO
Resistant therapy	EMAEP; VBP
FOLLOW-UP	
12 consecutive months of nondetectable hCG levels	
Contraception for 12 months	

ACT D, actinomycin D; EMACO, etoposide, methotrexate, actinomycin D, cyclophosphamide (Cytosan), vincristine (Oncovin); EMAEP, etoposide, methotrexate, actinomycin D, carboplatin; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MAC, methotrexate, actinomycin D, cyclophosphamide (Cytosan); MTX, methotrexate; VBP, vinblastine (Velban), bleomycin, carboplatin.

Stage IV

Table 12.5 outlines the NETDC protocol for the management of stage IV disease. All patients with stage IV disease should be treated with intensive combination chemotherapy and the selective use of radiation therapy and surgery. An 83% remission rate in patients with metastatic disease and a high-risk score has been achieved using EMACO, a combination regimen that includes etoposide, MTX, ACT D, cyclophosphamide, and vincristine (Oncovin). EMACO is currently the preferred treatment for patients with high-risk metastatic GTN. Combination chemotherapy is administered as frequently as toxicity permits until the patient attains three consecutive normal hCG values. After the patient achieves normal hCG levels, three additional courses of chemotherapy are administered to reduce the risk of relapse.

Unfortunately, the use of etoposide has been reported to increase the risk of secondary tumors including myeloid leukemia, melanoma, colon cancer, and breast cancer. The relative risk for leukemia, melanoma, colon cancer, and breast cancer was increased by 16.6, 3.4, 4.6, and 5.8, respectively, in patients who received more than 2 g/m². Etoposide should therefore be used only with high-risk metastatic disease. When patients with nonmetastatic and low-risk metastatic GTN experience resistance to MTX and ACT D, it is reasonable to consider administering triple therapy before the treatment with regimens containing etoposide.

Follow-Up

All patients with stages I, II, and III GTN should be followed with weekly hCG tests until normal for 3 consecutive weeks, and then monthly for

TABLE 12.5

TREATMENT PROTOCOL FOR STAGE IV GTN (NETDC, JULY 1965 TO JUNE 2006)

INITIAL
EMACO
With brain metastases—radiation; craniotomy for peripheral lesions
With liver metastases—embolization; resection to manage complications
RESISTANT
Salvage chemotherapy—EMAEP; VBP; Experimental protocols.
Surgery, as indicated
Hepatic artery infusion or embolization, as indicated
FOLLOW-UP
Weekly hCG levels until undetectable for 3 weeks, then monthly for 24 months
Contraception for 24 months

EMACO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; EMAEP, etoposide, methotrexate, actinomycin D, carboplatin; VBP, velban, bleomycin, carboplatin.

12 months. Patients should be encouraged to use contraception during the entire interval of follow-up. Patients with stage IV disease are followed with weekly hCG values until normal for 3 weeks and then monthly for 24 months. These patients require prolonged follow-up because they have an increased risk of late recurrence.

False Positive hCG Tests

hCG molecules in GTN are more degraded or heterogeneous in serum than they are in normal pregnancy. Trophoblastic disease samples contain high proportions of free β -hCG, nicked hCG, and β -core fragment. When monitoring patients with GTN, it is therefore desirable to use an assay that detects not only intact hCG, but also all of its metabolites and fragments.

Many hCG assays have a degree of cross-reactivity with luteinizing hormone. Following multiple courses of combination chemotherapy, ovarian steroidal function may be damaged, particularly in patients in their late 30s and 40s. When ovarian function is damaged, luteinizing hormone levels may rise, and owing to cross-reactivity, the patient may be falsely thought to have persistent low levels of hCG. Patients who receive combination chemotherapy should therefore be placed on oral contraceptives to suppress luteinizing hormone levels and prevent problems with cross-reactivity.

Some patients may also have a false-positive elevation in serum hCG measurement owing to the presence of circulating heterophilic antibody, called “phantom hCG.” These patients often have no clear antecedent

pregnancy and no progressive rise in their hCG levels. The possibility of false-positive hCG measurement should be assessed by sending both serum and urine samples to a reference hCG laboratory. Patients with phantom hCG generally have no measurable hCG in a parallel urine sample.

Quiescent GTN

Low-level “real” hCG has recently been recognized as a new clinical entity called quiescent GTN. In patients who have had a molar pregnancy or other type of GTN, the hCG level initially regresses, but persists at very low levels for many weeks or months. In these women, extensive workup reveals no lesion in the uterus or elsewhere, and administering chemotherapy is not effective. In this situation careful follow-up is recommended, since approximately 6% to 10% will ultimately relapse with rising hCG levels. At that point in time, chemotherapy will prove effective.

Recurrent GTN

Mutch and colleagues reported recurrences after initial remission in 2% of patients with nonmetastatic GTN, 4% of patients with good-prognosis metastatic GTN, and 13% of patients with poor-prognosis disease. Relapses developed within 3 and 18 months in 50% and 85% of patients, respectively. Most patients with stage I, II, and III GTN who develop recurrence are subsequently cured.

If patients experience resistance to EMACO, they may then successfully be treated with a modification of this regimen by substituting etoposide and cisplatin on day 8 (EMAEP). Bower et al. reported that EMAEP induced remission alone or in conjunction with surgery in 16 (76%) of 21 patients who were resistant to EMACO. Second-line therapy with cisplatin, vinblastine, and bleomycin or surgical intervention to remove the sites of drug-resistant tumor may also be effective in patients with drug-resistant GTN.

Subsequent Pregnancies

Pregnancies After Hydatidiform Mole

In general, patients with CHM and PHM can anticipate normal reproduction in the future. However, they are at increased risk of developing molar disease in later conceptions. An ultrasound should be performed in the first trimester of any subsequent pregnancy to confirm normal gestational development. An hCG measurement should also be obtained 6 weeks after the completion of any future pregnancy to exclude occult trophoblastic disease.

Pregnancies After GTN

Patients with successfully treated GTN can also generally expect normal reproduction in the future. The frequency of congenital malformations

or obstetric complications does not appear to be increased. Patients occasionally become pregnant before the recommended 12-month follow-up period has elapsed. When a patient's hCG level re-elevates after completing chemotherapy, the use of ultrasound enables the clinician to distinguish between an intercurrent pregnancy and disease recurrence.

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